# DARENTHIN
## HYPOTENSIVE AGENT OF NEW TYPE

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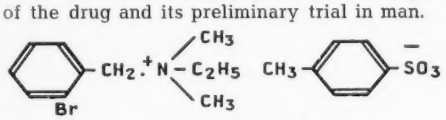
'Darenthin', *N*-*o*-bromobenzyl-*N*-ethyl : *N* : *N*-dimethylammonium *p*-toluenesulphonate, is a hypotensive agent with a new type of action. It is one of the series of benzyl quaternary ammonium compounds described by Boura et al. (1959) which selectively block the peripheral sympathetic (adrenergic) nervous system without antagonising the effects of released or injected adrenaline or noradrenaline. This block occurs without depression of the parasympathetic nervous system—a serious complication associated with the therapeutic use of ganglion-blocking agents—and also without central depression such as occurs with reserpine. The blocking effect of the drug on adrenergic neurones and its high specificity of action seem to be related to its selective accumulation in these neurones. This paper outlines the pharmacology of the drug and its preliminary trial in man.




Darenthin

While strictly speaking the name Darenthin* refers only to the *p*-toluenesulphonate salt, we shall for convenience use the term indifferently for the other salts examined.

### Experimental Pharmacology

Three salts of the cation were examined—*p*-toluenesulphonate, bromide, and iodide. No important pharmacological differences between the salts were found. Doses are stated in terms of base.

*Effects after Systemic Administration*

In cats the drug produced a generalised block of the sympathetic autonomic nervous system, peripheral to the ganglionic synapses. The adrenal medulla and the parasympathetic nervous system were unaffected, and the effects of injected adrenaline and noradrenaline were increased as after sympathectomy.

The blood-pressure of cats under chloralose anæsthesia fell gradually after the intravenous injection of doses of 0·5—5 mg. per kg. body-weight. With the lower doses the supine blood-pressure fell only slightly or not at all, but when the animals were tilted into a vertical plane postural hypotension was always pronounced (fig. 1), its extent increasing with the dose. After large intravenous doses, the hypotension was often preceded by hypertension. The hypotension can be explained by a generalised block of the sympathetic nervous system since it was accompanied by other manifestations of sympathetic block. For example, the cardiac acceleration caused by stimulation of the inferior cardiac branch of the sympathetic system was prevented, and the contraction of the nictitating membrane caused by stimulation of the cervical sympathetic nerve was abolished, irrespective of whether the stimulus was applied distal to or proximal to the superior cervical ganglion. The compound is not an adrenaline antagonist (adrenolytic); for, after its administration, intravenous injections of adrenaline and noradrenaline caused greater pressor responses and larger contractions of the nictitating membrane, as they do following sympathectomy. No effects on the parasympathetic nervous system were observed except for brief inhibitory effects, probably at the ganglion, after large intravenous doses. For example, the depressor effect of peripheral vagal stimulation, but not of injected acetylcholine, was reduced for a few minutes.

In unanæsthetised cats the nictitating membrane was relaxed by subcutaneous doses of 5-10 mg. per kg. body-weight and oral doses of about 30 mg. per kg. This relaxation is characteristic of substances that block the sympathetic system. The membrane was fully relaxed after 4-6 hours, and regained its normal tone only after 18-36 hours, according to the dose. No other effects were apparent; and, in particular, there was no behavioural disturbance such as occurs with reserpine, and no mydriasis or other manifestation of parasympathetic block such as occurs with all known ganglion-blocking agents. Large doses did not retard gastrointestinal propulsion in rats.

Unlike the ganglion-blocking agents, the drug did not block the pressor effect caused by activating the adrenal medulla by splanchnic-nerve stimulation. The catechol-amine content of the adrenals of rats or cats was not modified by daily administration of the drug during several weeks. Further, there was no significant change in the catechol-amine content of the sympathetic ganglia of the cats (superior cervical, stellate). A reserpine-like drug would deplete the adrenaline and noradrenaline content of the adrenals and sympathetic ganglia.

*Effects of Local Application*

Stimulation of the adrenergic nerves supplying various isolated smooth-muscle preparations ceased to be effective after the addition of a low concentration of the drug to the bathing fluid. Rather higher concentrations were needed to block the adrenergic nerve-trunks by topical application.

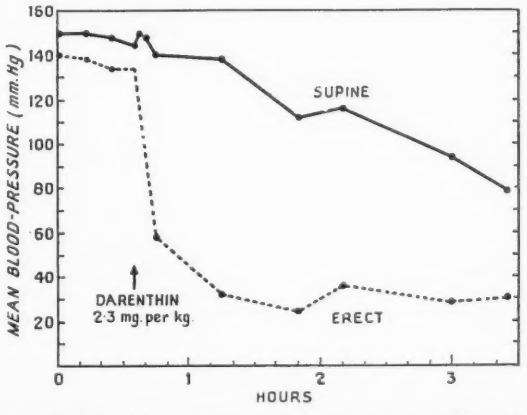



**Fig. 1—Effect of intravenous darenthin on the mean carotid blood-pressure of a cat under chloralose anaesthesia. The cat was supine except when tilted to an erect position until the fall of pressure was maximal.**

* Since this paper was written the approved name of bretylium tosylate has been allotted to darenthin.

Sensory nerve function could be blocked, but motor nerve-trunks to striated muscle appeared to be relatively insensitive.

The vasoconstriction in the perfused isolated rabbit ear caused by stimulation of the greater auricular nerve was abolished by the injection of 10—30 $\mu$g. darenthin into the perfusion fluid, whereas the vasoconstrictor effects of adrenaline and noradrenaline were increased. Similarly, a bath concentration of 1—10 $\mu$g. per ml. prevented the contraction of isolated rabbit uterus and the relaxation of rabbit duodenum caused by stimulation of their respective adrenergic nerve-supplies. The responses of both these preparations to either adrenaline or noradrenaline added to the bath were not inhibited. Adrenergic nerve stimulation ceased to have its usual effect on the isolated uterus and intestine when a concentration of 3—50 $\mu$g. per ml. was applied topically between the point of stimulation and the muscle.

*Distribution and Site of Action*

Darenthin (iodide), labelled with $^{14}C$ in one of its methyl groups, was injected subcutaneously into cats in a dose (6·6 mg. per kg. body-weight) sufficient to abolish sympathetic tone. When the animals were examined 3-18 hours later, much higher levels of radioactivity were found in sympathetic ganglia, postganglionic sympathetic fibres, and, in general, those organs with a rich adrenergic innervation than were found in the other tissues. The levels of radioactivity indicated that adrenergic nerves contained the drug at concentrations comparable to those which had been found to block adrenergic nerves when applied locally. This evidence supports the conclusion that darenthin impairs the function of adrenergic nerves and that its high specificity of action is related to preferential accumulation. No radioactivity was found in the central nervous system.

*Tolerance*

When large doses of darenthin (bromide) were injected daily in cats, the apparent reduction of sympathetic tone became progressively less. This is thought to be comparable with tolerance to the ganglion-blocking agents and the diminishing effectiveness of sympathectomy, which are both attributed to the development of increased peripheral sensitivity to adrenaline and noradrenaline.

In cats receiving large daily injections of the drug, the relaxation of the nictitating membrane became progressively less after a few days, just as it did after cutting the preganglionic cervical sympathetic nerve. Relaxation of the nictitating membrane passed off in cats within 2 weeks of cutting the left preganglionic cervical nerves. Then the injection of darenthin (bromide) did not affect the membranes on the operated side but completely relaxed the normal membranes. A ganglion-blocking agent showed a greatly diminished effect on the nictitating membrane in cats made tolerant to darenthin.

*Acute Toxicity*

The compound is toxic only when some thirty times the dose needed to reduce sympathetic tone is given, and then neuromuscular block is the probable cause of death.

A concentration of 30 $\mu$g. per ml. blocked the isolated phrenic-nerve-diaphragm preparation of the rat. In cats under chloralose anæsthesia, respiratory arrest usually followed rapidly after 20—30 mg. per kg. body-weight intravenously, and this was accompanied by depression of the gastrocnemius muscle contractions caused by stimulation of the sciatic nerve. Subcutaneously in unanæsthetised cats, 75 mg. per kg. caused severe muscular weakness but 38 mg. per kg. was well tolerated. In the monkey muscular weakness and ptosis were seen after 37 mg. per kg. subcutaneously.

*Chronic Toxicity*

Subcutaneous doses of 50 mg. per kg. of the bromide salt have been given daily for 4-6 weeks in rats, cats, and monkeys, without any cumulative toxic effect. Extensive histopathological studies carried out by Dr. V. Udall, and hæmatological and biochemical examinations by Dr. S. R. M. Bushby, have not revealed any change attributable to the drug. Oral doses of darenthin as high as 200 mg. per kg. (112 mg. per kg. of the base) in the monkey have been well tolerated now for 16 weeks.

**Trial in Man**

Pharmacological findings had shown that darenthin had potential clinical importance, by reason of its ability specifically to inhibit the peripheral sympathetic nervous system without either influencing the parasympathetic system or depressing the higher centres. Moreover, since the effects were reversed by adrenaline and other pressor amines such as methyl amphetamine, antidotes were readily available. With the satisfactory completion of toxicity trials, clinical investigations were begun.

*Methods*

Blood-pressures were all measured by auscultation at appropriate intervals. Standing blood-pressures were taken after 1 minute erect. Continuous electrocardiograms were recorded in the first few experiments. The bromide salt was used for all intravenous injections. The bromide, iodide, and *p*-toluenesulphonate salts have been used in the trials of oral administration. All seemed equally effective, but the bromide is hygroscopic, and to avoid possible toxic effects of bromide and iodide ions the *p*-toluenesulphonate was eventually substituted. Since clinical trial involved the use of these three salts, all doses have been converted into mg. of the base and are thus referred to below:

100 mg. darenthin (i.e., the *p*-toluenesulphonate salt) contains 56·0 mg. of the base.

100 mg. of the bromide salt contains 75·1 mg. of the base.

100 mg. of the iodide salt contains 65·6 mg. of the base.

It was eventually decided that scored compression-coated tablets containing 200 mg. of the *p*-toluenesulphonate salt (112 mg. base) would probably cover most needs. Doses were initially calculated on a mg. per kg. basis, but it soon became clear that this was not helpful.

EFFECTS IN NORMOTENSIVE VOLUNTEERS

*Intravenous Administration*

The first administration was into a running intravenous infusion of saline solution, to ensure that an exact dose of the drug had entered the circulation. The volunteer was given 0·37 mg. base per kg. body-weight (0·5 mg. of the bromide per kg.) over 30 seconds, with the intention of giving a second dose 2 hours later or not, according to the response. The subject was unaware that the drug had been given, but complained of palpitations and a sensation of retrosternal oppression immediately after the injection. Despite these symptoms there was no significant change in lying blood-pressure, which was recorded every 30 seconds at first, or in the pulse-rate or electrocardiogram. Animal experiments suggested the possibility of initial vasoconstriction which might have been related to these symptoms, and so later injections were given over 2 minutes with no recurrence of the symptoms. The subject remained supine for 2 hours, during which the blood-pressure, pulse-rate, and electrocardiogram did not change. A second injection of 0·37 mg. base per kg. was then given. Again there was no change until the subject sat up 90 minutes later, when the blood-pressure fell sharply and became unrecordable by auscultation. Postural hypotension persisted for 8 hours after the second injection.

Eight further intravenous injections were given to 4 volunteers. There was no effect on the supine blood-

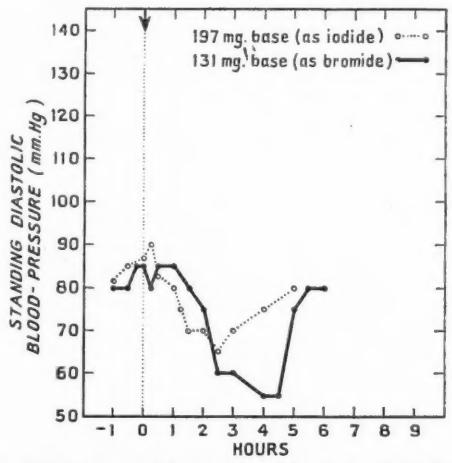



**Fig. 2—Effect of two oral doses of darenthin, given a fortnight apart, on the standing diastolic blood-pressure of a normotensive volunteer.**

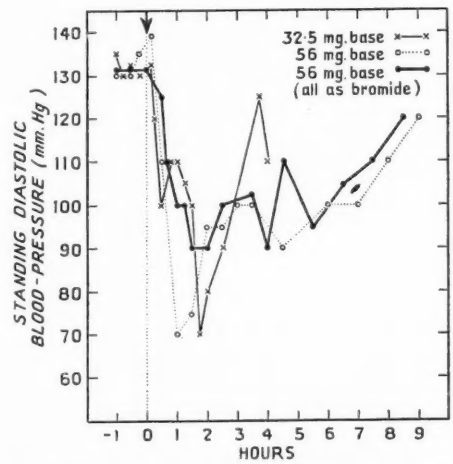



**Fig. 3—Effect of three intravenous doses of darenthin, given on successive days, on the standing diastolic blood-pressure of a hypertensive volunteer.**

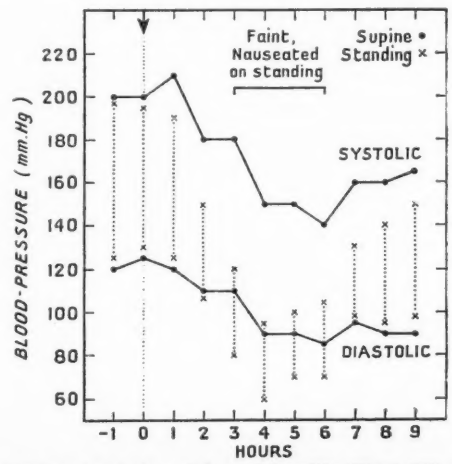



**Fig. 4—Effect of a single oral dose of darenthin 328 mg. (500 mg. of the iodide) on the blood-pressure of a hypertensive subject.**

pressure and no initial rise in blood-pressure such as had been found after large doses in the cat. Postural hypotension, commencing in 10 minutes and lasting for up to 5 hours, occurred in each of 3 subjects who received single doses of 53, 53, and 64 mg., but in another subject 53 mg. produced no effect.

Measurements of the circulatory response to Valsalva's manœuvre in a volunteer by Prof. A. C. Dornhorst confirmed that the drug produced effects characteristic of block of the sympathetic system. Intra-arterial infusion of 7·5 mg. in 3 subjects produced partial sympathetic block. The vasodilatation was preceded by vasoconstriction lasting about 20 minutes. This accords with the initial hypertensive effect of very large intravenous doses in cats.

*Oral Administration*

A total of sixteen experiments were performed on 10 subjects, giving the drug 1½—2 hours after the subject's normal breakfast. In no case was the supine blood-pressure significantly altered. Postural hypotension did not occur in either of two experiments in which 75 mg. of the darenthin base was given. In one experiment in which 131 mg. was given there was no effect, but in another there was considerable postural hypotension which lasted for 3½ hours. There was considerable postural hypotension in four, moderate postural hypotension in three, but no effect in five of the experiments in which 150—328 mg. was given. The variation in the response of different individuals did not allow any useful assessment of dose-response relations in the small number of experiments carried out. The onset of effects was from 1½ to 3 hours after administration of the drug and lasted for from 1 to 6 hours. Fig. 2 shows the response to two different doses a fortnight apart in the same subject.

These experiments showed that darenthin administered orally could produce postural hypotension lasting 6 hours without serious side-effects, and so its trial in hypertensive subjects was justified.

## EFFECTS IN HYPERTENSIVE SUBJECTS

*Intravenous Administration*

3 hypertensive subjects volunteered for intravenous doses of the compound. Five intravenous injections starting with 19 mg. and increasing to 75 mg. were given on different days to one subject. A moderate fall in the supine blood-pressure sometimes occurred, but this was less than the fall on standing. Pronounced postural hypotension, maximal at 1—2 hours and lasting for up to 8 hours, occurred after each of four doses of 37 mg. or more; the standing diastolic blood-pressures after three of these doses are shown in fig. 3. In another volunteer 75 mg. produced slight postural hypotension, but in a third 94 mg. did not alter the blood-pressure.

*Oral Administration*

Single doses of 197—328 mg. were given to 4 subjects. In 3 of them there was a considerable reduction in both the supine and standing blood-pressures (fig. 4). This started 1½—3 hours after administration of the drug and lasted up to 9 hours. In 2 of these subjects there was excessive postural hypotension with giddiness and nausea on standing, whereas the 4th subject showed only a very slight fall of blood-pressure after 328 mg.

The results of these experiments were sufficiently encouraging to warrant an attempt to control the blood-pressure in hypertensive subjects. Regular treatment, mostly with the *p*-toluenesulphonate salt, has been given for 1 to 26 weeks to 36 patients with moderate or severe hypertension, all with diastolic blood-pressures con-

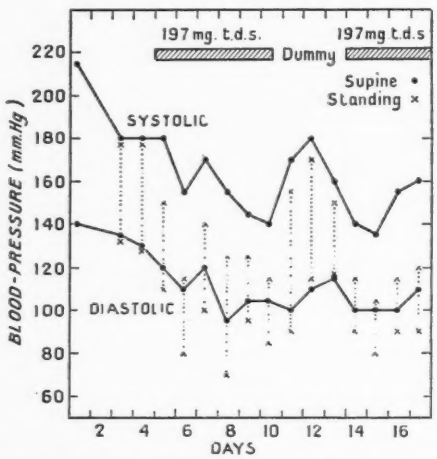



**Fig. 5—Effect of regular oral doses of darenthin on the blood-pressure of a hypertensive subject.**

sistently above 110 mm. Hg. The initial dose was 70—140 mg. three times a day, and this was altered according to the response of the patient. The dose of base required to control the blood-pressure varied greatly. One patient was satisfactorily controlled on 130 mg. three times a day, but another needed 840 mg. three times a day. Pronounced postural falls in both systolic and diastolic blood-pressure occurred in all the patients. The blood-pressure rose again in each of 4 patients when dummy tablets were substituted for the drug. Fig. 5 shows a typical response. Hourly blood-pressure records over 8 hours have shown that control is fairly smooth when the drug is given 8-hourly to these patients. There have, however, been several episodes of sudden severe postural hypotension, and we wonder if, for some reason, an unusually large proportion of a dose had suddenly been absorbed. Where large doses have been required, chlorothiazide has been added with apparent potentiation (4 cases).

10 of the 36 patients were started on darenthin as their first potent hypotensive agent, and control has been effective and trouble-free. 20 patients had previously been on other ganglion-blocking drugs; 5 had been on reserpine as well and this was continued, and their control on darenthin was, in every case, at least as good. In 4 patients although reduction of the blood-pressure was achieved, the drug was discontinued because of symptoms associated with postural hypotension. In a boy aged 12 with a bizarre adrenal abnormality only partial control of the hypertension was achieved with doses up to 420 mg. three times a day. The blood-pressure of one patient taking 840 mg. three times a day was not controlled despite the addition of 1 g. chlorothiazide daily. Doses larger than 840 mg. three times a day have not been exceeded, mainly because of the bulk of the tablets. A patient with malignant hypertension responded well to treatment (fig. 6) though he now needs 840 mg. three times a day together with 1 g. chlorothiazide daily. His fundi have shown much improvement, and he feels fit and is back at work.

*Side-effects*

Experience with this drug in man has confirmed the specificity found in the pharmacological experiments. There has been no impairment of parasympathetic function such as mars the use of ganglion-blocking agents, neither has there been any central depression such as occurs with reserpine. Patients who had previously been treated with ganglion-blocking agents were delighted at the absence of constipation. Side-effects have been trivial and attributable to sympathetic blockade. Stuffy nose, sometimes with complete nasal obstruction, occurred in twenty out of a total of twenty-five experiments in which the drug was given orally or by intravenous injection to normotensive volunteers. In the hypertensive patients, however, stuffy nose was not nearly so prominent, and when it occurred it was usually transient. An irregularity of pulse with dropped beats on standing occurred 4 hours after a dose of 197 mg. in 1 of the normotensive volunteers—it followed a large lunch and lasted for only an hour. Occasional dropped pulse-beats were noted during the intravenous injection of the drug in 1 patient only, but such effects have not been seen in patients given oral doses; 2 patients known to have angina suffered no discomfort.

*Absorption and Excretion*

Absorption studies of darenthin in man have been limited by difficulties in estimation, but animal experiments using $^{14}C$-labelled drug suggest that it is only partly absorbed from the alimentary tract. In keeping with this is the clinical impression that more of the drug is absorbed before breakfast on an empty stomach than if the same dose is given after breakfast. The urinary excretion of darenthin was followed in man by estimating, as their methyl-orange complex, those bases that were retained in 'Amberlite IRC—50' resin at pH5, but eluted by warm 0·5*N* HCl. Excretion in urine was fairly rapid after single oral doses of 197—328 mg. In 6 patients 10—30% of administered drug was recovered. No drug could be detected 24 hours after the dose. Absorption studies in man using the $^{14}C$-labelled drug are projected.

## Discussion

The effects of darenthin in the cat can be adequately interpreted as due to a persistent selective block of the postganglionic sympathetic nerves (adrenergic nerves), without interference with the effects of either adrenaline or noradrenaline on the effector organs. The same dose levels produced postural hypotension in man, and it can be concluded that a similar mechanism operates here.

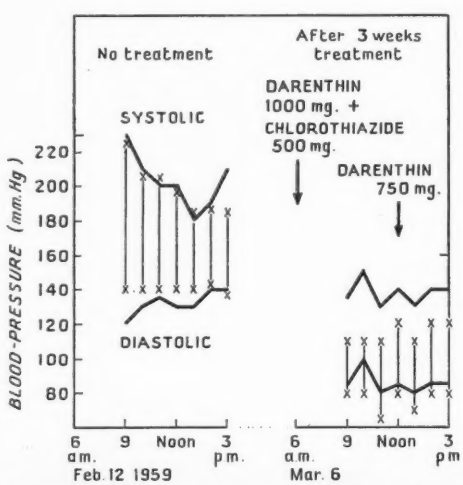



**Fig. 6—Hourly blood-pressure recordings in a patient with malignant hypertension before and during treatment with darenthin and chlorothiazide.**

While the whole adrenergic nerve appears to be susceptible to the drug, the blocking effect may be mainly at the nerve-endings. This is indicated by the finding that lower concentrations of the drug affected the response of isolated smooth-muscle preparations to adrenergic nerve stimulation when the drug was applied to the whole preparation than when it was applied solely to the nerve-trunk. Further, preliminary experiments in cats indicate that the doses needed to reduce the action-potential in adrenergic nerve-trunks exceed the doses abolishing the responses of the end-organ to nerve stimulation.

The pharmacological properties more closely resemble those of the 2:6-xylylether of choline bromide, TM 10 (Hey and Willey 1954, Exley 1957), than those of any other known pharmacological agent, but there are important differences. TM 10 has marked parasympathomimetic properties which have precluded its use in man as a hypotensive agent (D. Taverner, cited by Bain and Fielden 1957); such properties are not shown by darenthin. Unlike TM 10, darenthin did not deplete the pressor-amine content of the rat adrenal, neither did it reduce the stores of catechol amines of the tissues when it was administered for several weeks to cats. Consequently, we consider that it does not act by depleting the local stores of catechol amines nor by inhibiting the biogenesis of noradrenaline—the mode of action postulated for TM 10 (Bain and Fielden 1957, Coupland 1958).

A study of the effects of large doses of darenthin on the nictitating membrane of cats indicates the possibility of tolerance developing as after ganglion blockade. It seems likely that tolerance does occur in man, but so far this has not been a serious problem. The pratice of starting with a small dose of the drug and gradually increasing the dose one to three times a week would mask minor degrees of tolerance. However, patients stabilised in hospital on a dose of darenthin may require increased dosage over succeeding weeks as outpatients. Over the same period none of these patients has needed to reduce the dose.

Since noradrenaline, and to a lesser extent adrenaline, has a greater pressor effect following darenthin, and since, unlike the ganglion-blocking agents, darenthin does not block the mechanism of release of these catechol amines from the adrenal medulla, the activity of the adrenal medulla may be expected to influence blood-pressure and various sympathetic functions to a relatively greater extent after administration of the compound. Very severe hypertension developed in a patient with phæochromocytoma after the cautious intravenous administration of 53 mg.

Sufficient evidence has been obtained to justify the wider study of the action of darenthin in man, and its possible application in therapeutics. The drug has controlled severe hypertension when given by mouth. The dose is relatively large and the amount required varies considerably in different patients, but the response has been relatively constant in individual patients, and control of blood-pressure has been well maintained through the day. Slight tolerance probably occurs. The great advantage of darenthin is its highly specific action on the sympathetic nervous system, unaccompanied by any of the impairments of parasympathetic function which are so troublesome with ganglion-blocking agents. It is suggested that a reasonable initial oral dose is 200 mg. of the *p*-toluenesulphonate (112 mg. base) three times a day, this to be increased under supervision not faster than by the addition of 100 mg. of *p*-toluenesulphonate to each dose every day.

**Summary**

'Darenthin', *N*-*o*-bromobenzyl-*N*-ethyl : *N* : *N*-dimethylammonium *p*-toluenesulphonate, is a hypotensive agent of novel type. In animals it selectively blocks the peripheral sympathetic nervous system by action on the adrenergic nerves, in which it selectively accumulates. It does not inhibit the effects of circulating or injected adrenaline or noradrenaline. It has no apparent effect on the parasympathetic or central nervous systems.

Its effect on man has been studied in healthy volunteers and evidence of sympathetic block obtained.

In hypertensive patients it lowers the supine blood-pressure slightly and causes postural hypotension at doses which produce only trivial side-effects.

The oral dose is about five times the minimal dose effective by intravenous injection. The hypotensive response to oral administration varies between different patients, but in the individual patient the response is fairly regular and control is evenly maintained throughout the day.

The compound deserves more extensive clinical trial in the treatment of hypertension.

Our thanks are due to the volunteers who assisted in the trial of 'Darenthin'. We are indebted also to Dr. F. C. Copp for the provision of $^{14}C$-labelled drug, and to Dr. W. G. Duncombe for the determinations of radioactivity.

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## INTERRELATIONS OF TOLBUTAMIDE AND GLUCAGON

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DESPITE much experimental work on the sulphonylurea compounds the mechanism of their hypoglycæmic action has not yet been elucidated. As opposed to the generally accepted hypothesis that the fall in blood-glucose is due to an increased supply of insulin by the pancreas, some studies (Anderson et al. 1956, Recant and Fischer 1957) have suggested that it may be the result of a diminished glucose output from the liver. The explanation offered originally by German workers that these drugs inhibit the production of glucagon by the pancreatic $\alpha$-cells (von Holt et al. 1956) has not been confirmed. It has been shown, moreover, that glucagon elicits a hyperglycæmic response even during sulphonylurea treatment (Franke and Fuchs 1955).

Anderson et al. (1957) reported that the hyperglycæmic response to glucagon was intensified by tolbutamide. They interpreted this as indicating a deficiency of endogenous glucagon and a consequent hypersensitivity to exogenous glucagon. They also claimed that patients whose rise in blood-glucose after glucagon is normal or higher than normal are unlikely to respond to the sulphonylureas. Izzo and Roncone (1957) have reported that the "sugar-raising effect of glucagon could be quantitatively antagonized or counterbalanced" by the administration of a sulphonylurea compound (carbutamide).

The work of Anderson et al. (1957) and Izzo and Roncone (1957) suggested that the relation of glucagon to the sulphonylureas should be examined afresh.

### Patients and Methods

12 patients over fifty years of age with diabetes of recent onset were selected as suitable for sulphonylurea treatment. 9 (cases 1—9) responded well to tolbutamide, and 3 (cases 10—12) did not.

The studies were carried out after an overnight fast. Capillary blood was drawn by fingerprick, and the glucose-content was estimated by the Herbert and Bourne (1930) modification of the Folin and Wu method. 400 μg. glucagon (Elli Lilly batch no. 0358 PA—60923) was injected intravenously, and further capillary blood-samples for glucose-determination were taken after twenty, forty, sixty, and eighty minutes. This procedure was repeated the next day after a dose of 3 g. tolbutamide had been given by mouth three hours before the glucagon injection. During both tests the patients were recumbent, and they had been asked to avoid any unnecessary movements.

### Results and Discussion

The results are shown in the accompanying figure.

In 6 patients (cases 1 — 5 and 12) the rise in blood-glucose induced by glucagon was almost identical in both tests. Only 1 of these 6 patients (case 12) did not eventually respond to tolbutamide.

3 patients (cases 6, 7, and 11) showed a greater response and 3 (cases 8 — 10) a lesser response to glucagon in the second test. 1 patient in each of these two groups (cases 10 and 11) did not respond satisfactorily to tolbutamide.

Studying only the initial tests, it can be seen that there is no significant difference between the response of the 9 patients who were eventually successfully treated with tolbutamide and the 3 patients in whom treatment was unsuccessful.

Liver glycogen is broken down to glucose partly by the enzyme phosphorylase. The hyperglycæmia which follows the administration of adrenaline and of glucagon is the result of increased hepatic glycogenolysis; and both these hormones are believed to induce this by influencing the phosphorylase enzyme system. The increased release of glucose from the liver raises the glucose-level in the hepatic vein; and it also leads to a higher arterial glucose-concentration. The increased glucose output is reflected in the extent of the rise in blood-glucose as well as in the duration of the rise, though the duration is also influenced by the rate of peripheral glucose disposal.

In earlier work (Weaver et al. 1958) we were unable to show that tolbutamide has any effect on the peripheral utilisation of glucose, measured by the arteriovenous glucose difference or by the rat-diaphragm technique: it therefore seems reasonable to attribute the difference in arterial glucose-concentration after glucagon and after glucagon plus tolbutamide to differences in hepatic glycogenolysis.

This study does not indicate that tolbutamide consistently impairs the stimulating effect of glucagon on hepatic glycogenolysis. Conversely, we were unable to demonstrate that previous tolbutamide administration accentuates the response to glucagon.

The effect of glucagon on patients who responded well to tolbutamide and on those who did not was similar.

These conclusions concern only the hepatic response to exogenous glucagon: they do not exclude the possibility that tolbutamide affects hepatic glucose release or even the response to endogenous glucagon.

### Summary

The effect of tolbutamide on the response to glucagon has been studied in 12 diabetic patients. The capacity of glucagon to raise the blood-glucose was unaffected by the preliminary administration of tolbutamide.

We wish to thank Dr. J. A. Smyth, who was physician-in-charge of the metabolic unit during the period of this study.

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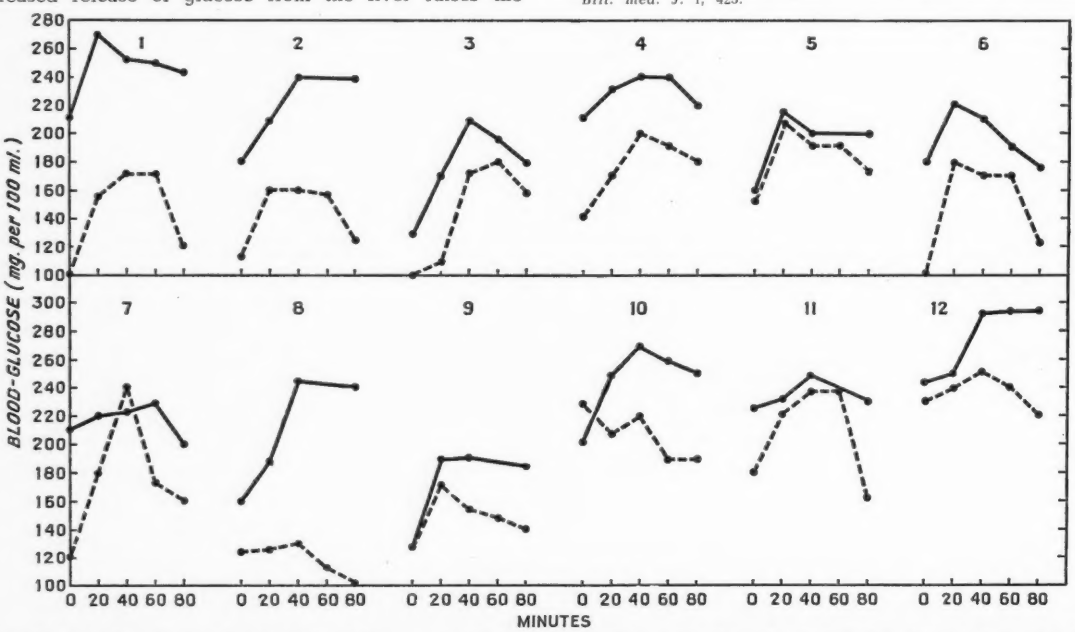


**The effect of glucagon on the arterial blood-glucose concentration before and after tolbutamide administration in 12 diabetic patients. The continuous line shows the changes after glucagon alone (test 1); the interrupted line the changes after tolbutamide and glucagon (test 2).**

# DIAGNOSTIC CORTICAL BIOPSY
## A HISTOLOGICAL AND CHEMICAL STUDY

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A HISTOLOGICAL study of 27 cerebral biopsies, taken to determine or to confirm the clinical diagnosis, was reported by one of us (Blackwood 1955) at the 2nd International Congress of Neuropathology. An exact diagnosis was possible in a third of the cases. In biopsies taken since, a part has been examined chemically, and the additional information has enabled a definite diagnosis to be made more often. A preliminary report on the combined examination of 30 specimens was given last year (Blackwood and Cumings 1958). We have now examined 65 such biopsies, and we record the results here.

### Material and Methods

The biopsies were taken from a presumably diseased cerebral hemisphere, and usually from the frontal lobe. 56 were from children or young adults with increasing mental disability—which was regarded as essential to justify this procedure—and 9 were from adults with dementia. In all patients the biopsy was for diagnostic purposes, and none was any worse for the operative procedure.

The biopsy was removed through a 3·15 cm. trephine hole. The surgeon was asked to remove a single cube of tissue, with sides at least 1·5 cm. long, including both white and grey matter. The, specimen was placed unfixed, in a widemouthed container, and taken immediately to the laboratory. Some specimens were sent from other hospitals, in which case the container was packed in dry ice, and sent by the most rapid method available. When the specimen had to be kept overnight before dispatch, it was stored in a deep freeze (—20°C), then next day packed in dry ice, and forwarded with all speed.

In the laboratory the specimen was divided into two; one part was fixed in 10% formol-saline and examined histologically, while the other was examined chemically. We were told the age and the main clinical features of each patient, and we made independent diagnoses.

The histological methods employed were:

*Frozen.*—Scharlach R and hæmatoxylin, toluidine blue mounted in microil, and periodic-acid Schiff (P.A.S.) and hæmatoxylin.

*Paraffin.*—Hæmatoxylin and eosin, and hæmatoxylin and van Gieson. When indicated Gros Bielschowsky or Da Fano's impregnation for neurofibrils, Mallory's P.T.A.H. or Cajal's gold-sublimate method for astrocytes, Anderson's victoria blue for astrocytic fibres, Hortega's silver impregnation for microglia, Loyez stain or Sudan black for myelin, and Lendrum's phloxine-tartrazine stain for inclusions, were employed.

The histological diagnosis of the lesions found was based on well-recognised features (Greenfield et al, 1958).

The chemical examinations which were carried out have already been described (Cumings 1953, 1957). They included estimations of total phospholipids, total and esterified cholesterol, hexosamine, neuraminic acid, and water content. The results were interpreted on the basis of previous findings on necropsy material (Cumings 1957).

### Results

In 36 cases a definite diagnosis could be made. In some the histological and chemical examinations were in agreement; in others only one method was diagnostic. The different methods gave apparently conflicting diagnoses only once. Table I shows the results.

TABLE I—RESULTS OF HISTOLOGICAL AND CHEMICAL EXAMINATION OF 65 BIOPSY SPECIMENS

| Condition | Diagnostic abnormalities | | Abnormal but not diagnostic | | Normal or no significant abnormality | |
|---|---|---|---|---|---|---|
| | Histology | Chemistry | Histology | Chemistry | Histology | Chemistry |
| Normal | .. | .. | .. | .. | 23 | 23 |
| Amaurotic family idiocy | 9 | 10 | .. | 4 | 5 | .. |
| Metachromatic leucodystrophy | 4 | 7 | 1 | .. | 2 | .. |
| Sudanophilic diffuse sclerosis | 2 | 2 | .. | .. | .. | .. |
| Multiple sclerosis | 1 | 1 | .. | .. | .. | .. |
| Subacute encephalitis | 6 | .. | .. | 6 | .. | .. |
| Tuberose sclerosis | 2 | .. | .. | 2 | .. | .. |
| Organic dementia of adult life | 6 | . | .. | 8 | 2 | .. |
| Conflicting opinions | 1 | 1 | .. | .. | .. | .. |
| Unknown | 1 | 1 | .. | .. | .. | .. |

It will be seen that of the 65 biopsies, 23 showed no abnormality either histologically or chemically. Of the remaining 42, 36 yielded a positive diagnosis by one or both methods of examination.

TABLE II—COMPARSION OF HISTOLOGICAL AND CHEMICAL OPINIONS GIVEN IN AMAUROTIC FAMILY IDIOCY AND METACHROMATIC LEUCODYSTROPHY

| Condition | Diagnostic abnormalities | | Abnormal but not diagnostic | | Normal or no significant abnormality | |
|---|---|---|---|---|---|---|
| | Histology | Chemistry | Histology | Chemistry | Histology | Chemistry |
| Amaurotic family idiocy | Cases 1-9 | Cases 2-8, 10-12 | .. | Cases 1, 9, 13, 14 | Cases 10-14 | .. |
| Metachromatic leucodystrophy | Cases 1-4 | Cases 1-7 | Case 5 | .. | Cases 6, 7 | .. |

The results in amaurotic family idiocy and in metachromatic leucodystrophy (table II) are given separately to show when the methods were in agreement, and when histological examination was not diagnostic.

### Discussion

23 biopsies showed no significant abnormality by any of the methods we used. This does not exclude the possibility that other or newer methods of investigation might show abnormality, or that a piece of brain removed from another site might have been abnormal. We can only state that, under the conditions of this investigation, these biopsies appeared to be normal.

We have used the convenient term amaurotic family idiocy to cover all four varieties of the disease—Tay-Sachs' disease, late infantile, juvenile, and the adult form. Typically amaurotic family idiocy involves most of the nerve-cells of the cortex. In the early stages the changes in each individual nerve-cell are slight, making a positive histological diagnosis difficult. But the increase in ganglioside is easily detected chemically, and is rarely found in any other condition in children.

Metachromatic leucodystrophy is another condition with widespread abnormality, but one which affects the white matter. Here again the chemical changes are more readily detected than are the early histological lesions, and this no doubt is why 7 cases were diagnosed chemically, but only 4 histologically.

In subacute encephalitis and tuberose sclerosis the histological changes can be specific and diagnostic even when they are only slight. The chemical changes were not diagnostic of either condition. In both cases of tuberose sclerosis, however, the changes were obvious to the naked eye. In subacute encephalitis the histological features were those of van Bogaert's subacute leucoencephalitis, or inclusion-body encephalitis, but in none of the cases examined were inclusions found. Chemical examination showed some loss of phospholipids, together with an increase of total hexosamine.

The organic dementias of adult life comprised 5 cases of presenile dementia or Alzheimer's disease, with, histologically, Alzheimer's neurofibrillary change and argyrophilic plaques; 1 case of vascular disease, with a small zone of ischæmic necrosis; 2 cases without histological abnormality; and 1 case of multiple sclerosis with dementia. In the first 8 of these chemical findings showed some abnormalities, of which the most striking was an increase in ganglioside in the cerebral cortex. This has been found in all cases of dementia of adult life, the figure for ganglioside usually being higher than that for a normal person of corresponding age. The 9th patient with dementia was found chemically to have multiple sclerosis.

There were conflicting opinions in only 1 case. Histologically the features were those of amaurotic family idiocy, but chemically the findings indicated a demyelinating condition of the sudanophilic diffuse-sclerosis type. This patent later died, and through the kindness of Dr. Alexander Shapiro, of Harperbury Hospital, we were able to examine the brain.

Histologically there was a very considerable loss of nerve-cells from the cerebral cortex, and many of the remaining nerve-cells throughout the brain were distended with sudanophilic, P.A.S.-positive, isotropic material. Much of the subcortical white matter was replaced by phagocytes containing sudanophilic lipid and anisotropic crystalline material. These histological changes in the white matter were comparable with the chemical changes, which showed a very considerably increased amount of esterified cholesterol. Hence a chemical diagnosis of sudanophilic diffuse sclerosis was confidently made. The reduced neuronal population in the cortex may possibly account for the low ganglioside level found chemically in that region.

This case of lipid-storage disease in the nerve-cells of the brain was unusually severe, though a few similar cases are mentioned by Greenfield et al. (1958).

The case labelled "unknown" showed in the subpial zone numerous phagocytes containing a little sudanophilic lipid and anisotropic crystalline material. Similar phagocytes were present in the white matter, but here myelin destruction was only slight. The loss of nerve-cells was not significant. Chemically the presence of esterified cholesterol indicated active demyelination in the white matter. There was also a considerable increase in the hexosamine content of both the white matter and the cortex. Such an increase is most commonly found in metachromatic leucodystrophy, but the presence of esterified cholesterol made it more likely that the condition was a sudanophilic diffuse sclerosis; in view of the conflicting chemical findings and the indefinite histological changes, a firm diagnosis was not possible.

These findings show that in 3 biopsies out of every 4 in which some abnormality was present, a positive diagnosis was possible by a combined chemical and histological approach. Many of the conditions mentioned are difficult to diagnose clinically, and are familial in nature; therefore any new approach which aids diagnosis and is not injurious to the patient is, in our opinion, valuable.

**Summary**

The results of histological and chemical examination of small pieces of cerebral tissue removed at biopsy from 65 patients with progressive dementia are reported. In 3 out of every 4 abnormal biopsies it was possible to make a definite diagnosis. The method is therefore recommended as a valuable aid to diagnosis.

We wish to thank the physicians and surgeons, too many to name individually, for their kindness in sending us material, and in providing clinical data. Our technical colleagues, Mr. H. Goodwin, Mr. A. Greenaway, and Mrs. P. Kelman-McConnachie, deserve special praise for their very careful and helpful assistance.

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## NUCLEAR CHROMATIN OF ANENCEPHALIC FOETUSES

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Most anencephalic fœtuses have female external genitalia. Female external genitalia were found in 90% of Potter's (1953) series; and female preponderance was reported also by Zander (1890) (2:1), Ballantyne (1904) (3:1), Covell (1927) (5:1), and Hilman (1953) (4:1). These fœtuses have abnormalities of the endocrine glands, the best known being a small adrenal cortex. The anterior pituitary gland was at one time thought to be absent. Ballantyne (1904) was unable to demonstrate this gland in most of his 45 cases; but later investigators (Covell 1927, Angevine 1938) found it in every case, though it was very small. The experiments of Jost (1953), in the rabbit, have shown the importance of the fœtal pituitary gland in the functional development of the fœtal testes and in their control of the normal masculinisation of the genital tract.

These observations suggest that some anencephalic fœtuses with female external genitalia might be chromosomal males, which had failed to become masculinised owing to the abnormality of the pituitary gland. If this were so, it would explain the high proportion of "females" in this condition. I have investigated this aspect of anencephaly by relating the nuclear chromatin to the phenotype.

A series of 24 anencephalic fœtuses was collected. A skin biopsy was taken from the anterior abdominal wall of each fœtus and fixed in formol saline. Each piece of tissue was sectioned at 8 $\mu$, and stained with hæmatoxylin and eosin, and the nuclei of the epidermal cells were examined for the Barr chromatin mass (Barr and Bertram 1949, 1951).

Of the 24 fœtuses 21 (87%) had normal female external genitalia. These 21 were all chromatin-positive.

Of the 24 fœtuses 3 (12%) had male external genitalia. They were all chromatin-negative.

### Discussion

It is of great interest to find that in anencephaly the abnormality of the pituitary gland, which may be presumed to explain the smallness of the fœtal adrenal gland, has not resulted in any cases of sex reversal with failure of masculinisation of the genital tract.

There is thus still no clear explanation for the great preponderance of females in this abnormality.

**Summary**

Of 24 anencephalic fœtuses 87% showed female external genitalia.

The nuclear chromatin pattern corresponded in all cases to the genital sex.

I wish to thank Prof. E. W. Walls for help and advice in the preparation of this paper, and the many pathologists and obstetricians who made available the anencephalic fœtuses for this study.

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# Preliminary Communication

## CHRISTMAS-FACTOR (FACTOR IX) DEFICIENCY PRODUCED BY CONCURRENT ADMINISTRATION OF HEPARIN WITH COUMARIN DRUGS

THE purpose of this communication is to draw attention to the risk of heparinising a patient who is receiving a coumarin drug.

A woman about to undergo an operation for atrial septal defect using a pump oxygenator was treated with a coumarin drug (phenindione, "Dindevan") up to the day before her operation and came to operation with a prothrombin-time subsequently found to be 28·5 sec. (normal control 12·8 sec.). She was heparinised in the usual way with 2 mg. heparin per kg. body-weight intravenously, and the surgical procedure was completed without complication. On attempting to neutralise the heparin with protamine sulphate at the end of the procedure, however, it was found that little or no neutralisation was being achieved although many times the usually effective dose of protamine was administered. The blood was incoagulable in vitro (Lee and White technique). Continuous oozing from all parts of the operative field persisted, and the patient died some hours later. Subsequent studies showed a hæmophilia-like state with a severe Christmas-factor deficiency.

This case suggested a potentiating effect of heparin on the deficiency or deficiencies produced by coumarin drugs, and experimental evidence of such an effect was therefore sought.

### EXPERIMENTAL STUDIES

Five rabbits, fed on a stock diet with vegetables and water ad lib., were given a small dose (1·0 mg. per kg. body-weight) of heparin intravenously. Blood was taken five minutes later for coagulation studies. The animals were then given a three-day course of dicoumarol (Abbott)—6 mg., 4 mg., and 2 mg. by stomach tube on successive days. On the fourth day blood was taken for coagulation studies before and five minutes after administration of heparin in the same dose as that given initially.

I had previously found that the Christmas-factor defect resulting from parenteral heparin[1] depends on dosage. A small enough dose will produce no abnormality in the thromboplastin-generation test, although prolonging the clotting-time.

In the present investigation I found that, in the dosage used, the initial dose of heparin prolonged the clotting-time (mean 100 min.) and single-stage prothrombin-time, but had no effect on thromboplastin generation. The course of dicoumarol produced no change in the clotting-time (mean 9 min.) but, as would be expected, a very prolonged single-stage prothrombin-time. The thromboplastin-generation test now showed a severe serum-factor defect, which was shown by mixing experiments to correspond to a Christmas-factor defect. The effect of the dose of heparin on the dicoumarolised animal was to render the blood incoagulable. The clotting-time tubes did not clot at all, nor did the single-stage prothrombin tests, with or without heparin antagonists such as protamine or toluidine-blue. The thromboplastin-generation test now showed a more severe Christmas-factor defect in the serum than was found in the dicoumarolised animals before the injection of heparin.

1. O'Brien, J. R. *Nature, Lond.* 1958, **181**, 1801.

### STUDIES IN MAN

We have studied two further patients who were about to undergo open heart surgery and who were under treatment with a coumarin drug. In view of our previous experience, we stopped treatment with the coumarin drug a week before the day of operation. Twenty-four hours after the last dose of coumarin drug, heparin therapy by deep subcutaneous injection was commenced to maintain anticoagulation until the operation. Coagulation studies were carried out while the patient was still on the coumarin drug, and daily after the inception of heparin treatment until the day of operation. When heparin therapy was started a severe serum-factor defect corresponding to a Christmas-factor defect appeared. Thromboplastin-generation tests on both patients while on the coumarin drug showed only slight serum defects (85% and 65% generation).

Serial studies showed that, in about five days, the serum defect had disappeared in both cases; but specimens taken on the day of operation while the patients were anæsthetised, but before heparin was given, showed a slight Christmas-factor defect. This was greatly increased in both cases on injection of heparin (2 mg. per kg. body-weight). After protamine-sulphate neutralisation (on a mg. for mg. basis) the defect had disappeared in one patient (who now had a normal thromboplastin-generation test) but not in the other. Clinical bleeding in this second case tended to be excessive in the first twenty-four hours postoperatively, although clotting-times were within normal limits.

### DISCUSSION

A deficiency of Christmas factor has been observed in the serum of some patients receiving coumarin drugs.[2-5] In such cases the glass clotting-time (Lee and White) is usually within normal limits. Augmentation of this defect by administration of heparin and the production of a hæmophilia-like state does not seem to have been reported previously.

O'Brien[1] has shown that heparin, added to the thromboplastin-generation test in vitro, causes defective thromboplastin generation, which, however, can be corrected by addition of more serum to the reaction mixture. Serum from cases of Christmas disease does not have this corrective effect. This I have confirmed and find that thromboplastin generation in the presence of minute amounts of heparin is a very sensitive test for Christmas-factor defect. Testing a series of patients on coumarin drugs I have found that their sera do not correct the defective thromboplastin generation in a heparinised reaction mixture (unpublished). Shanberge et al.[6] have shown that protamine sulphate added to the reaction mixture of the thromboplastin-generation test also induces a Christmas-factor defect.

2. Sise, H. S., Kimball, D. M., Adamis, D. *Proc. Soc. exp. Biol., N.Y.* 1955, **89**, 81.
3. Greig, H. B. W., Tattersall, J. C. *Brit. J. Hæmatol.* 1956, **2**, 421.
4. McElfresh, A. E., Ozge, A. J. *Lab. clin. Med.* 1957, **49**, 753.
5. Douglas, A. S. *J. clin. Path.* 1958, **11**, 261.
6. Shanberge, J. N., Barlase, A., Regan, E. E. *J. Lab. clin. Med.* 1958, **52**, 744.

The practical importance of this observation in relation to open-heart surgery is obvious. Patients on coumarin drugs who are to undergo surgery requiring heparinisation should be taken off the coumarin drug at least one week before the operation. Whether vitamin K will rectify this Christmas-factor defect as it does the acquired Christmas-factor defect in liver disease (Greig, unpublished) I have not ascertained.

My thanks are due to Mr. D. Adler and Mr. D. N. Fuller for permission to study their cases, and to the Director of this Institute for facilities for carrying out this work.

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## Reviews of Books

### T. H. Huxley: Scientist, Humanist and Educator

CYRIL BIBBY, M.A., M.Sc., Ph.D., F.L.S. London: Watts. 1959. Pp. 338. 25*s*.

IN 1842 Apothecaries Hall held an open competition in botany for a silver medal. On the day of the examination, at four o'clock, the end of the time allowed for the written paper, no objection was raised to a request that candidates might be allowed to complete their answers, instead of stopping at once. Four hours later, a young apprentice from Ealing was still writing, and to such effect that, in the face of a number of University-coached competitors, he carried off the prize. Thomas Henry Huxley had publicly demonstrated for the first time the intellectual vigour and physical indefatigability destined to make him one of the most powerful influences on scientific thought in his century.

He is today remembered most often as the creator of the School of Science and the Natural History Museum, at South Kensington, and as "Darwin's Bulldog", who championed the theory of evolution in a battle of theological and scientific controversy which was fought with a bitterness that a later generation finds hard to comprehend. But he did much more than this: his views shaped the whole pattern of elementary and technical education in this country, and exerted on it an effect felt from dockside schools in Liverpool to Eton College (of which he became a governor). It was he who coined the word "agnostic" to describe his own religious views, and who founed the periodical, *Nature*, which, paradoxically, he intended to be a magazine for the general public.

Huxley's initial training was as a doctor—he served an apprenticeship at Rotherhithe, and then won a scholarship to Charing Cross Hospital. He never completed his M.B. degree, however, but in 1846 entered the Royal Navy as an assistant-surgeon and, embarking on *H.M.S. Rattlesnake*, began the researches on marine biology which first brought him scientific fame. But if he never practised medicine, he nevertheless had a profound influence on the profession—as a member of such commissions as that which shaped the Medical Act of 1886, and as a sponsor of men like Michael Foster, who was appointed, by way of a post for which Huxley recommended him, to the chair of physiology at Cambridge.

In this biography, Dr. Bibby has paid attention to all the facets of Huxley's impressive personality, and the book is fully annotated, with a detailed list of references (even the dates on which Huxley began cigarette-smoking, changed to cigars, and took up a pipe). But this high standard of scholarship nowhere obtrudes on the style of a book to be highly recommended.

### A System of Orthopædics and Fractures

A. GRAHAM APLEY, M.B., F.R.C.S., consultant orthopædic surgeon, Rowley Bristow Orthopædic Hospital, Pyrford, Surrey. London: Butterworth. 1959. Pp. 357. 47*s*. 6*d*.

FOR many years, there has been held at the Rowley Bristow Hospital, Pyrford, a comprehensive course in orthopædics and fractures designed primarily for aspirants to the surgical fellowship. An important feature of this course has been the notes, issued to each student "as a prophylactic against writer's cramp". So much in demand were these notes that their author, Mr. Graham Apley, decided to make them available in a bound and edited form. The book could have been a bare synopsis of its subject, unacceptable to any save examination candidates: in fact, because there is no suggestion of the staccato in the writer's style, and because he discusses even the lesser known features and treatments of each lesion, the volume is an easy and profitable one for any doctor to read. Though it is a little too large for a hip pocket, it is readily carried in the hand; and the publishers have chosen wisely in providing a pliable but sturdy binding for a book that is certain to be much consulted by many readers.

### Nutrition and the Public Health

H. E. MAGEE, M.B. Belf., D.Sc., M.R.C.P., formerly senior medical officer (nutrition), Ministry of Health. London: Pitman Medical Publishing Co. 1959. Pp. 151. 25*s*.

This is a useful little book, which provides an account of the elementary principles of nutrition and can be recommended to laymen and ancillary medical workers with a special interest in public health. Dr. Magee has had long experience both as a laboratory worker and as an administrator. He is thus able to give a concise account of the basic physiology of metabolic processes. This is followed by a general account of public-health methods in nutrition, and there are chapters on food additives and chemical residues, on diet and disease, and on dietary surveys.

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**Advances in Virus Research, vol. VI** (New York and London: Academic Press. 1959. Pp. 382. £4).—Of the seven reviews in this volume, edited by K. M. Smith of Cambridge and M. A. Lauffer of Pittsburgh, three deal with the purification, biochemistry, and spread of plant viruses, one with bacteriophage genetics, one with kappa particles in paramecium, one with the purification and properties of poliovirus, and one with measles virus. They are mostly very detailed, bursting with information, and difficult to read. If reviews of this kind are to serve a purpose beyond that of bringing the writers up to date with the literature in their chosen field, it seems important that those who write them should have the courage to sacrifice completeness for the sake of some clarity and simplicity. Thus, the very fascinating subject of bacteriophage genetics is dealt with rather uncompromisingly by S. Brenner, while T. M. Sonneborn's chapter on paramecium requires as much devotion from the reader as it must have required from its author. The chapters on measles (F. L. Black, M. Reissig, and J. L. Melnick) and poliomyelitis viruses (F. L. Schaffer and C. E. Schwerdt) are not quite so heavy and contain much useful information.

**Surgical Pathology** (St. Louis: C. V. Mosby. London: Henry Kimpton. 1959. Pp. 1096. 112*s*. 6*d*.)—Now in its second edition, this work from the Washington University School of Medicine at St. Louis must be one of the most beautifully (not merely lavishly) produced medical books of today. All the illustrations have been carefully chosen for their photogenicity as well as for their didactic value; they are superbly reproduced; and they are more numerous than the printed pages. This in itself would make the volume a desirable addition to any library; but the text, too, is sound and informative if in places somewhat pedestrian. Pathologists in this country may find it especially useful as a guide to the Transatlantic usage of terms such as "cancer". On the other hand, like most writers of textbooks, the authors often cover up (instead of drawing attention to) vast gaps in our knowledge: and, in view of the dual authorship by a pathologist (Prof. Lauren V. Ackerman) and a surgeon (Dr. Harvey R. Butcher, Jr.), it is perhaps a pity that the contradictions between pathological teaching and surgical practice have not been given greater prominence.

**New and Nonofficial Drugs** (Philadelphia: J. B. Lippincott. London: Pitman Publishing Co. 1959. Pp. 687. 30*s*.).—The new *N.N.D.* contains 42 more pages than last year, and 41 new monographs on drugs ranging from chlorambucil to triacetyloleandomycin. As usual it is a valuable guide to drugs approved by the Council on Drugs of the American Medical Association which are commercially available in the United States, but not necessarily included in the pharmacopœias.

THE LANCET

LONDON 11 JULY 1959

## Adrenergic Blockade

The medical treatment of severe and malignant hypertension is at present based on the family of drugs which block transmission at the synapses of the autonomic ganglia. These drugs have structural features in common with acetylcholine, and the presumption is that they compete with acetylcholine at the receptor sites of cholinergic action. It follows from this that they will block cholinergic transmission in general; in addition to their valuable action in blocking preganglionic sympathetic impulses, they also block both preganglionic and postganglionic parasympathetic action. It is this parasympathetic block which accounts for most of the side-effects which the ganglion-blocking agents have in common; in addition, there are side-effects peculiar to individual members of the group, such as mecamylamine, which are based on special properties of the particular drug, such as the penetration of mecamylamine into the body-cells, and not on the ganglion-blocking action itself. Because of the relative ubiquity of cholinergic transmission, the search for a drug which will selectively block sympathetic action at the ganglionic level seems doomed to failure; but postganglionic sympathetic transmission is adrenergic, and adrenergic blockade would be expected to be free from side-effects based on parasympathetic inhibition. Direct antagonists of adrenaline and noradrenaline, such as phentolamine, do not significantly lower the blood-pressure in essential hypertension, although they are of course active in those patients with phæochromocytoma whose hypertension is due to circulating noradrenaline and adrenaline. Nevertheless, if a drug were selectively accumulated in adrenergic nerve-endings, it could attain a local concentration sufficient to block adrenergic transmission, while not antagonising the direct action of circulating adrenaline or noradrenaline.

A drug with just these properties seems now to have been developed in bretylium tosylate ('Darenthin'). BOURA, COPP, and GREEN[1], of the Wellcome Research Laboratories, described a series of benzyl quaternary ammonium compounds " which selectively block the peripheral sympathetic (adrenergic) nervous system without antagonising the effects of released or injected adrenaline or noradrenaline ". One of these compounds is *N*-*o*-bromobenzyl-*N*-ethyl : *N* : *N* dimethyl ammonium, which can be given as bromide, iodide, or *p*-toluenesulphonate, the last form being bretylium tosylate. On an earlier page we publish a preliminary, but detailed, report prepared jointly by the pharmacologists who developed the drug and the clinicians who carried out clinical trials in the medical unit of University College Hospital. By combining the pharmacological and clinical observations in one paper, the authors have made it possible for the interested clinician to be aware not only of the effects so far observed in man but also of those which may be likely to occur when the drug is in general use.

The animal studies indicate a generalised block of the sympathetic nervous system, with relaxation of the nictitating membrane in cats, and inhibition in the rabbit of vasoconstriction in the ear, uterine contraction, and duodenal relaxation caused by stimulation of the adrenergic nerve-supply. The amount of drug which caused these effects was not associated with any evidence of parasympathetic inhibition, of interference with the central nervous system, or of failure of intestinal propulsion. When much larger amounts of the drug were given, there was generalised neuromuscular block, which caused severe muscle weakness and death in acute toxicity experiments. Studies with labelled bretylium tosylate showed that the explanation of the high specificity of the drug at the lower dose-level lay in selective accumulation within adrenergic nerves. The drug was not adrenolytic, and so did not block the pressor effect of splanchnic stimulation of adrenal output; in fact, the response to injected adrenaline and noradrenaline was increased, as happens after sympathectomy. The clinical observations in normal volunteers and in hypertensive patients show that the effects in man are in general those to be expected from the animal work; and that the drug can be used for the long-term control of severe hypertension. As with the ganglion-blockers, the effective dose varies considerably in different patients, ranging from 130 mg. t.d.s. to 840 mg. t.d.s. in the 24 patients so far observed; and the dose had to be adjusted, as tolerance developed. Constipation and side-effects due to parasympathetic inhibition were absent, and there was no depression such as occurs with reserpine. Side-effects so far have been trivial; most of the normal volunteers were troubled by nasal congestion, but this was not nearly as prominent in the hypertensive patients.

These studies show that in bretylium tosylate we have a drug of great intrinsic interest, and also of great promise for the practical treatment of severe hypertension. The new drug is not, of course, a cure for hypertension, any more than the ganglion-blockers were; and the absence of crippling side-effects should, for the present at least, be regarded as a boon to those patients who have to be treated by hypotensive agents on currently accepted indications, not as an invitation to extend these indications widely.

1. Boura, A.L.A., Copp, F.C., Green, A.F. *Nature, Lond.* 1959, (in the press).

## A Companion for Isoniazid

Isoniazid is an almost ideal drug for treating tuberculosis: it is taken by mouth, the effective daily dose is relatively small, it is cheap, and it has very few side-effects. But there is no ideal companion for it: streptomycin, although effective, cannot easily be self-administered, and *p*-aminosalicylic acid (P.A.S) has important disadvantages. The amount required daily—10 to 20 g. of sodium (P.A.S)—is too large to be conveniently taken in tablets; abdominal discomfort, depression of appetite, and diarrhoea may be troublesome; and it is expensive for long-continued treatment. Its bulk and unpleasantness may, as has been suggested, be important reasons for irregular medicine-taking by patients out of hospital, although forgetfulness probably plays a large part. Attempts to make it more acceptable have been unsuccessful. The calcium and potassium salts have been tried, as have various presentations of the sodium salt and compounds such as benzoyl P.A.S., phenyl P.A.S., and a P.A.S. resin. Some give adequate serum P.A.S. concentrations; others do not, except in doses too bulky to be acceptable. None of them, moreover, are without side-effects and all are expensive.

In countries with well-developed health services and a high standard of living it is not impossible to treat patients with daily injections of streptomycin for long periods and not too expensive to use P.A.S. But the great majority of patients with tuberculosis are in less favoured countries; and for them, if indeed any treatment at all is possible, cheap, non-toxic oral drugs are essential. The British Medical Research Council, recognising the great importance of a good companion drug for isoniazid in such circumstances, have been carrying out investigations in East Africa, and the result of one was published early this year.[1] The companion drug was diaminodiphenylsulphone (D.D.S.), which has some therapeutic action in man, is cheap, relatively non-toxic, and already extensively used for leprosy. Unfortunately, the results were disappointing. Although clinically the combination of isoniazid and D.D.S. was only slightly inferior to isoniazid and P.A.S. over the trial period, it failed to prevent emergence of isoniazid-resistant strains of tubercle bacilli. The emergence of resistant strains is of course, the most important criterion by which a treatment should be judged; and a combination leading to about 40% of patients excreting isoniazid-resistant strains after six months' treatment of acute pulmonary tuberculosis is unacceptable. The prevalence of resistant strains in East Africa appears to be already high, presumably because of inadequate chemotherapy in the present and the past. In this study, for instance, almost 1 in 10 of the patients originally admitted to the trial had isoniazid-resistant cultures before hospital treatment began. The urgency of the search for an isoniazid companion and the need for strictly controlled field studies giving unequivocal answers in the shortest time amply justify the minute risks of adding to the further spread of resistant organisms by such clinical trials.

Other oral drugs have been tried. A substituted thiourea, thiocarbanidin, is being studied in the Veterans Administration chemotherapy trials in the U.S.A. The substance, as at present administered, appears ineffective in preventing isoniazid resistance. In France some preliminary clinical work has been carried out with alpha-ethyl-thioisonicotinamide. In vitro this thioamide is reported to be approximately twice as active as streptomycin.[2] In man it appears to have some effect on pulmonary tuberculosis[3]; but so far there is very little information about its action when given with isoniazid to previously untreated patients. On the present evidence the drug is unlikely to replace P.A.S., for in the dosage so far used (1 g. daily) it has caused unpleasant gastrointestinal symptoms in a high proportion of patients.[3,4] Of the 102 patients treated by BROUET and his colleagues[3] only 55 had no symptoms of intolerance: malaise, anorexia, nausea, and vomiting were recorded as severe or very severe in 36, and 5 patients could not tolerate it at all. Further trials are at present being carried out in this country by the Research Committee of the British Tuberculosis Association.

1. East-African/British Medical Research Council Sulphone Investigation. *Tubercle, Lond.* 1959, **40**, 1.

## Hospital Chimneys

IN 1955 the Minister of Health decided that a new general hospital of 516 beds should be built at Wythenshawe, an expanding residential area of Manchester. The planning was well advanced when a serious hitch arose. The Manchester city corporation are firmly resolved to do away with atmospheric pollution, not only to obtain " clean air " by removing the visible pollutants (such as smoke and grit) but eventually to attain pure air by removing invisible pollutants (such as sulphur dioxide), thus going beyond the requirements of the Clean Air Act of 1956. The only fuels which do not pollute the atmosphere are gas and electricity; and the corporation, who own the site for the new Wythenshawe Hospital, refused to lease it to the Minister unless he agreed to the use of gas or electricity for heating, lighting, and steam production. Because of the extra expense of these fuels, the Minister has not acceded to this demand; and as a way out of the deadlock the Manchester Regional Hospital Board now propose that a smaller hospital of 360 beds should be built on an adjacent site which already belongs to him. For a hospital built on this latter site, the fuel used would have to comply only with the provisions of the Clean Air Act, thus defeating the more radical purpose of the Manchester corporation.

Important issues are raised by this disagreement. The Minister no doubt fears that if he assents to the

2. Rist, N., Grumbach, F., Liebermann, D. *Amer. Rev. Tuberc.* 1959, **79**, 1.
3. Brouet, G., Marche, J., Rist, N., Chevallier, J., LeMeur, G. *ibid.* 1959, **79**, 6.
4. Somner, A. R., Ross, J. D. MacLeod, H. M., Stewart, S. M., Horne, N. W., Crofton, J. W. *Brit med. J.* 1959, i, 486

use of gas or electricity in the new hospital he will set a precedent not only for all new hospitals but for *all* hospitals, whereby the fuel cost of the National Health Service could become positively crippling. Since expenditure on the service is covered by a general grant from Parliament, we can appreciate his dilemma; for the figures quoted by his advisers suggest that the cost of electricity would be six times higher than that of coal or oil, and the cost of gas about three times higher. On the other hand, the Manchester corporation have ample reason for their belief that pure air should be the chief public-health objective of this generation. In Manchester and similar industrial cities, bronchitis is endemic; and from December to March, inflamed by superadded smog and respiratory infections, it does great damage. Last winter the hospitals were overwhelmed; and it must have been ironical to see their own chimneys polluting the air of wards crowded by patients with pneumonia, asthma, bronchitis, emphysema, and cor pulmonale. Unfortunately, purification of the air cannot be attained without sacrifice and almost revolutionary determination: everyone must be convinced of its importance — the industrialist, the householder, the owner of car, bus, and lorry, and the smoker. But surely, the corporation argue, the first person from whom they might expect support in their battle is the Minister of Health. For health, like peace, is indivisible, and here is an excellent means of showing that ours is not merely a National Sickness Service.

Perhaps the Minister's financial fears are not so soundly based as his advisers have supposed. Though it can be very bad in smaller cities situated in valleys which retain the impure air, such as Sheffield, atmospheric pollution is generally worst in the great conurbations like Manchester and Glasgow. (Manchester is surrounded by large industrial towns, each with its smoke pall; and, whichever way the wind blows, the city is polluted.) Could not a start be made in the hospitals of these densely industrialised areas; and, if so, how better than with a brand-new hospital? The expense may not in fact prove prohibitive; for, as the Town Clerk of Manchester has pointed out, the figures presented to the Minister do not accurately reflect present-day overall costs, taking into account the saving in capital charges, transport, storage, cleaning, and the like. Moreover, the general price trends suggest that in a few years' time the cost of electricity will be no greater than that of other fuels — perhaps much less when electricity is largely derived from nuclear energy.

The Wythenshawe Hospital and the adjacent Baguley Hospital will include one of the main chest centres for the Manchester region. Even if the new hospital to be built at Wythenshawe is to rise on the very suitable site already owned by the Minister, would it not be an act of statesmanship to identify the prevention of chest diseases with the same programme as their cure?

# Annotations

## QUEEN MARY'S AND THE FOUNTAIN

In celebrating its fiftieth anniversary the other day [1], Queen Mary's Hospital for Children could hardly be jubilant; for its future was very much in doubt. Having suggested a year ago that this hospital should close, and that the Fountain Hospital should be moved into its buildings, the Minister of Health showed no sign of having changed his mind. But the alternative plan he has now put forward not only ensures Queen Mary's continuation as a general children's hospital but makes it the scene of an interesting innovation.

This fine modern hospital, at Carshalton in Surrey, has 550 functional beds (of which about 400 are usually in use) and another 150 in reserve [2]. But under the same regional hospital board is the Fountain Hospital at Tooting, which houses 600 mentally defective children [3] in unsuitable premises which should properly contain no more than half the number; and the contrast between the circumstances of these two institutions has been painfully obvious — at any rate to everyone who cares about the Fountain. Since rebuilding of the latter at a cost of £2-3 million is not yet held to have priority among capital schemes, the Ministry thought last year that the best way of using the board's resources would be to distribute Queen Mary's present patients among other institutions and convert its buildings, at relatively small expense, to the needs of The Fountain. This, however, meant that many of the children of that part of London, who can at present count on admission to a first-rate children's hospital, would in future have to go into small children's units in general hospitals, or even into adult beds; and this was so plainly a piece of retrogression — undertaken for financial rather than medical reasons — that it rightly evoked widespread opposition. Under the Minister's new plan Queen Mary's, with its important training school, which provides 15% of the annual entry for the Register of Sick Children's Nurses [2], will remain a general children's hospital; but in about eighteen months' time — or sooner if possible — it will take 120 children from The Fountain into its empty villas. Later the total of children transferred from Tooting may rise to 300 or 350; but it should be possible for The Fountain to continue its national contribution to treatment, research, and teaching with a centre on or near its present site. The need for a large new building for this purpose remains as plain, and as urgent, as before.

What is encouraging is that one upshot of these events and discussions may be a kind of hospital, new to this country, which will accept on one site children who are physically ill and children who are mentally ill. The Ministry and the board have turned difficulties to good account by making this practical advance towards the more comprehensive type of hospital, with separate but related sections, which seems likely to be the right pattern for the future practice of medicine. Here, clearly, is something for which it is worth making concessions, and taking risks, and working under inconvenience; and we hope that the management committees of both hospitals are ready to make the best of what may in fact turn out to be a very good job. Particularly encouraging has been the response of the nurses at Queen Mary's to the request that they should spend part of their training in the care of The Fountain's defectives.

1. *Lancet*. 1959. i, 1214.
2. Lawson, D. *Ibid*. 1958, ii, 263
3. *Ibid*. 1959, i, 420

## SLIPPED UPPER FEMORAL EPIPHYSIS

CONFIRMATION of slipping of the upper femoral epiphysis depends on radiography. Displacement is usually seen most clearly in lateral radiographs; and, as Jerre[1] has shown, quite severe displacement may be completely masked by changes in the projection of the hip. Standardisation for the comparison of films is essential, and the technique described by Billing[2] provides a relatively simple method of assessing the position of the femoral head. The object of the positioning is to ensure that the radiographic beam passes through the plane of the epiphyseal plate. This can normally be achieved by a frontal view in which the leg is rotated internally 20°. Occasionally internal rotation is impossible, and the film must be marked accordingly so that subsequent views are comparable. The lateral view of the femoral neck is taken with the femur rotated externally and flexed 25°. When the angle of anteversion of the femur is large the leg is better positioned some 20° short of full external rotation.

Billing and Severin,[3] after comparing the head with the development of the acetabulum, suggest that slipping of the epiphysis begins during the year before the Y-shaped cartilage ossifies, and is thus more closely related to skeletal development than to chronological age. Slipping, they believe, occurs only dorsally and is followed by remoulding of the femoral neck, bone being absorbed ventrally and deposited dorsally. The displacement of the femoral head is often expressed in terms of the movement of the epiphyseal cartilage along the metaphysis. This method, as Billing and Severin point out, is valueless in the presence of metaphyseal moulding, since the original position of the epiphysis can no longer be assessed. Because the slipping of the epiphysis occurs along the arc of a circle its displacement can also be measured as an angle. This angle is not affected by metaphyseal moulding, and a concealed slip may be demonstrated in this way. Brailsford[4] suggested that there is a preslipping stage in which the metaphysis is widened but the head is undisturbed.

Radiographs of the femoral neck after nailing in situ showed that, although ossification and fusion of the epiphyseal cartilage was the usual result, in some cases the neck continued to grow. In these cases there is clearly a risk of further displacement. In some the nailing may have been inadequate; but the promotion of ossification by a single nail may be slow, and at times uncertain. In the fixation of the femoral head two or three pins are probably less traumatic, and more certain.

From the answers to a questionary circulated to orthopædic surgeons, Burrows[5] confirmed that in boys the left hip is more commonly affected than the right, although the same is not true for girls. In about a quarter of the patients both hips were affected. Girls presented at an earlier age than boys, and apparently by the menarche the female is relatively immune to this disorder. The results of treatment in the patients (with the addition of some others) enabled Hall[6] to survey 173 hips. This review shows that only occasionally can the displacement be reduced by traction, even supplemented by medial rotation, unless there is a history of a recent acute episode. In such cases manipulation by medial rotation commonly reduced the deformity, but was associated with a risk of avascular necrosis. The results of simple nailing of the displaced epiphysis were good, but the results of fixation with multiple pins were much better. Cervical osteotomy was followed by aseptic necrosis of the femoral head in 38% of patients, and without internal fixation was almost uniformly disastrous.

The displaced upper femoral epiphysis was discussed by the British Orthopædic Association at its spring meeting this year. A. M. Rennie suggested that the angulation of the upper femoral epiphysis was due to diminished growth posteriorly following minor trauma, and that the displacement was secondary to this; whilst R. Soeur believed that the cause was purely mechanical. With an acute slip the displacement can often be reduced by gentle manipulation, and the position of the head maintained by internal fixation, and both P. H. Newman and J. and R. Judet reported good results of treatment in this way. There was general agreement that in patients with a gradual displacement it was better to accept the position and to guard against further displacement by pinning. Some of the resulting deformity could be corrected by a late subtrochanteric osteotomy, without the risk of avascular necrosis which so often follows cervical osteotomy. Many speakers commented on the unsatisfactory results of this operation, and H. G. Lowe pointed out that the prognosis of avascular necrosis depended on whether the articular cartilage as well as the femoral head was involved. Avascular necrosis is a major problem in the displaced upper femoral epiphysis, and it is more often due to the treatment than to the disease.

1. Jerre, T. *Acta orthopæd. scand.* 1950, suppl. 6.
2. Billing, L. *Acta radiol., Stockh.* 1954, suppl. 110
3. Billing, L., Severin, E. *ibid.* 1959, suppl. 174, p. 7.
4. Brailsford, J. F. The Radiology of Bones and Joints. London, 1953.
5. Burrows, H. J. *J. Bone Jt Surg.* 1957, **39B**, 641.
6. Hall, J. E., *ibid* p. 659.

## THE EDINBURGH DIAGNOSTIC CENTRE

Many of us believe that if the general practitioner is to remain a good doctor he must more often make his own diagnoses—and act upon them. For a sufficient examination of the patient, he sometimes needs equipment which few surgeries possess; and various arrangements are now being tried by which he can make fuller use of modern diagnostic procedures. The latest of a series of experiments supported by the Nuffield Provincial Hospitals Trust is the Family Doctor Centre in Edinburgh, whose object is to stimulate the practitioner's clinical interest and give him all the facilities for diagnosis and for follow-up to which he was accustomed during his training.

Opened on June 1, the centre is in converted premises, owned by Edinburgh University, at the Livingstone Dispensary, and thus adjoins the university's general-practice teaching unit. It affords a wide range of diagnostic procedures, including laboratory, X-ray, and electrocardiograph equipment, with the necessary technical, nursing, and clerical staff—together with a social worker when required. With the title of honorary medical adviser, Dr. W. A. Alexander, formerly senior physician to the Edinburgh Royal Infirmary, is prepared to help practitioners in their use of specialised diagnostic procedures, and, where necessary, to see cases in consultation with them. But there is no intention that specialists should consult at the diagnostic centre: it is, indeed, fundamental to the experiment that practitioners shall carry the diagnosis as far as possible with their own skill and the resources provided, and that, though they can have guidance from the medical adviser, they shall retain full responsibility for their patients. At present there are five consulting-rooms, and only about 40 practitioners have the right to make bookings at the centre. Selection by ballot, and restriction of the period of tenure, have been necessary in the first instance because the applicants were greatly in excess of capacity; but room for more way soon be found.

The Department of Health for Scotland have taken a leading part in this project. The General Medical Services Subcommittee (Scotland) and the Edinburgh Local Medical Committee, representing the general practitioners of Edinburgh, have given their support, as have the Consultants and Specialists Committee, Scotland. The other principal partners in the venture are the South-Eastern Regional Hospital Board and the University of Edinburgh.

## RESTORATION OF SPEECH AFTER LARYNGECTOMY

THE development of speech is peculiar to man, but the primary function of the larynx in all stages of its evolution is to protect the entrance to the pulmonary airway by means of its valvular sphincter, so it is incorrect and misleading to speak of the larynx as *the* organ of voice. The larynx is a highly complex structure capable of producing an almost infinite variety of sounds with different pitch, loudness, and colour. It has been justly observed that only talented singers and trained actors make use of more than a fraction of the available range, and the vast majority of people use their voice almost in a monotone.[1] Everyday speech depends more on the intact articulating mechanism of the mouth, nose, and pharynx, with its central connections, than on the function of the larynx.

The loss of the larynx is nearly always the result of radical surgery for malignant disease. With suitable preparation before operation and tuition afterwards most patients acquire an alternative method of speaking by "œsophageal" voice. There are several techniques for producing this voice and most patients finally develop an individual way of speaking. Air is taken into the œsophagus during inspiration, with the cricopharyngeal sphincter relaxed, and then released from the œsophageal reservoir against the contracting sphincter. The column of air is thus set vibrating and the note so produced is articulated into speech in much the same way as when the basic note is produced in the larynx. A high degree of fluency and clarity may be achieved by this method, and œsophageal speech is the ideal to strive for after every total laryngectomy. Because of the character of the operation or of the patient, or an associated disease, however, a hard core of patients are unable to acquire this speech; and such patients would have to remain permanently mute were it not for help from various artificial sources of sound, from which they may fashion a voice.

The artificial larynx is the simplest aid and has been available for many years. One end of an angulated tube containing a reed is placed in the tracheostomy, the other in the mouth; the current of expired air vibrates the reed and the resulting sound is formed into words in the mouth. As all the articulation has to take place in the anterior part of the oropharynx, intelligibility is usually poor. Moreover, the instrument is cumbersome, unsightly, and unhygienic, requiring frequent dismantling to clear it of mucus. It has never been widely used because of these disadvantages, and it is now being displaced altogether by recent developments in electronic appliances. One of its modern counterparts incorporates a transistorised oscillator in a pocket-sized pack. Sound is directed into the mouth from a small microphone fused to a plastic tube, and both volume and pitch are variable. This device overcomes most of the snags of the old artificial larynx, but it costs $200.

The second group of appliances are the vibrators, where the sound is produced by an electrically operated vibrating diaphragm, and external vibrators have been in use for some years. When the diaphragm is pressed against the soft tissues just under the lower jaw, part of the sound is conducted into the mouth and pharynx. Normal articulation converts this into monotonous speech of reasonable intelligibility. The voice is produced against a background of fairly loud unmodulated noise from the vibrator. Experiments with variable frequency patterns have so far failed to produce a reliable aid. The instruments require rather large batteries to vibrate the diaphragm, they are rather cumbersome to use, and their cost is high. Mr. MacGregor's suggestion (in a letter on p. 38) is to construct a collar pattern to hold the instrument against the neck so that the patient's hands are free. In spite of some of their drawbacks, external vibrators have been of great service in promoting rehabilitation after laryngectomy and allowing patients to resume work more quickly, while still learning œsophageal speech. Dr. Armitage Whitman, a New York surgeon, has used one for five years and found it a "veritable miracle" in helping him to continue in practice.[2]

To overcome some of its defects the vibrator principle has recently been adapted by carrying the source of sound directly into the mouth. The advantage of the oral vibrator is that all the sound is generated where it can be used for voice production, resulting in highly intelligible speech. The device is relatively inconspicuous and requires no special cleaning or maintance. The frequency of the sound may be varied so that vocal inflexions and a better modulated speech are possible. Mr. Tait has devised an electromagnet diaphragm unit (to which he refers on p. 38) enclosing an air space and attached to the upper denture or artificial palate.[3] This diaphragm is connected by a fine flex cable to a small transistorised oscillator housed in a small box with its batteries. This electric circuit may conveniently be worn in the pocket and supplies current to the electromagnet in the mouth, whereby the diaphragm is vibrated to produce sound. A similar approach has been used by Cooper and Millard,[4] who analysed the resulting speech with a special cineradiographic unit incorporating image intensification and a sound spectrograph. The speech was at least as satisfactory as that produced by good œsophageal speakers.

Conley et al.[5] have devised a new surgical treatment. A small mucosal or skin tunnel, or a free vein graft, is used to connect the upper œsophagus with the tracheostome. This tunnel curves steeply upwards and forwards from the œsophageal opening and collapses on swallowing, so that spill-over of œsophageal contents into the trachea is prevented. A specially adapted tracheostomy tube is used with a connecting outlet fitting into the tunnel. Intermittent obstrucion of the external opening of the tracheostomy tube then directs a stream of expired air into the cervical œsophagus and pharynx where it may be used for voice production. Preliminary assessment showed that the technique of œsophageal speech was acquired early and effortlessly, and a number of patients were later able to speak without using the tunnel. Its continued presence in the neck seems to have been no handicap. Extension of this method may well provide satisfactory unaided speech for many who would otherwise fail to acquire a new voice after laryngectomy. At this stage, however, the electronic aids are the only reliable alternative for those patients who cannot acquire intelligible œsophageal speech. These devices are especially helpful when an extensive operation is to be followed by a long programme of reconstruction or when early return to work is imperative.

1. Negus, V. E. The Mechanism of the Larynx. London, 1929.

2. *Pfizer Spectrum*, 1957, **5**, 439.
3. Tait, R. V. *Brit. dent. J.* 1959, **106**, 336.
4. Cooper, H. K., Millard, R. T. *Dent. Digest.*, March, 1959.
5. Conley, J. J., de Amesti, F., Pierce, M. K. *Ann. Otol., &c., St. Louis*, 1958, **67**, 655.

## Occasional Survey

# RELAXIN
## A REVIEW OF CLINICAL PROGRESS *

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RELAXIN, the third member of the hormonal triumvirate of pregnancy, modifies the pelvic joints of many lower animals (Sands 1958a), and similar changes in the pelvic joints of pregnant women can easily be detected (Sands 1958b). The relationship of relaxin to other hormones of pregnancy is shown by two observations: in castrated animals which have been maintained on progesterone, relaxin will increase uterine responsiveness to oxytocin (Steinetz et al. 1957); and in cattle which have been given œstrogens it will increase the ease with which the cervix can be dilated (Graham and Dracy 1953). The hormone can also increase glycogen, total nitrogen, and water content of uterine muscle (Steinetz et al. 1957).

Relaxin, which is not a steroid, is a protein or a polypeptide, soluble in water, and highly stable. It has been demonstrated in the blood of pregnant women, increasing in concentration to the 38th week and disappearing rapidly within 24 hours of parturition.

### Use in Medicine

Boucek (1955), using his "sponge biopsy" technique, studied the histochemical characteristics of pure connective tissue of different ages. When the host was treated with relaxin the older connective tissue took on features of a younger type. Collagen fibres became finer and more widely separated, the ground substance was depolymerised, mast cells increased in number, and there was an increased imbibition of fluid—all fundamental changes.

When it was observed that the skin of relaxin-treated animals became very loose, Casten and Boucek (1958) used the hormone in scleroderma for which there had previously been no consistently satisfactory treatment. They treated twenty-three patients for over 3 years, and found that skin tightness decreased, trophic ulcers healed, and Raynaud's phenomenon was relieved. Evans (1959) obtained even better results and in one patient an ulcer healed which had resisted treatment for over 29 years. Similar results were reported by Rogoff and Rivelis (1958). Evans found that in many instances bougie dilatation for dysphagia could be stopped, and in other cases joint movements and the respiratory complications of scleroderma improved.

This improvement with relaxin exceeded that achieved with corticosteroids. Unfortunately, the corticoids block the activity of relaxin.

Noble and Boucek (1958) working with "sponge biopsies" found that the concentration of cholesterol was lower in connective tissue from relaxin-treated animals than in tissue from controls. Further investigation showed that it was the rate of cholesterol synthesis which was modified by relaxin. Attempts to produce similar results by thyroid ablation, or by feeding thyroid to hypothyroid animals, were unsuccessful, and tetraiodothyroacetic acid, progesterone, or testerone were equally ineffective. Using $^{14}C$-labelled acetate they showed that only relaxin was able to reduce the rate of cholesterol synthesis in the connective tissue of both sexes. These results are interesting in view of the present-day increase in the proportion of elderly in the population ,and also in view of the relationship between blood-cholesterol and atherosclerosis.

Relaxin has also been tried in peripheral vascular diseases. Casten (1958) was able to increase claudication time, raise skin temperatures, heal intractable ulcers, increase muscle output, and improve trophic changes in the skin and nails of the limb.

Relaxin seems to benefit the coronary circulation, and it has also relieved postradiation hepatobiliary fibrosis. Experimental work on these lines is in progress (Molander and Sands 1958). Relaxin is also being used in the treatment of keloidosis and it seems that keloid formation is slightly lessened.

All these actions of relaxin are on connective tissue.

### Use in Obstetrics

Since relaxin softens the connective tissue of which the cervix is chiefly composed, its effectiveness was studied in patients selected for induction who had an "unfavourable" cervix.

*Induction of Labour*

At or near term, the management of the patient with an unfavourable cervix is difficult, because the uterus seems peculiarly unresponsive to oxytocics. In one series, however, relaxin enabled labour to be successfully induced in 71·5% of such cases, compared with only 22·8% in controls given pitocin stimulation alone (Stone et al. 1958). Relaxin was given intravenously as a solution of 120 mg. in 500 ml. of 5% glucose solution, injected at the rate of 4 ml. per minute. 4 hours later intravenous pitocin was started in the usual dosage. This method is now being evaluated in Boston and the preliminary results are encouraging.

*Duration of Term Labour*

In one series (Birnberg and Abitbol 1957) labour was reported to be remarkably shortened by relaxin. Our own results have been surprisingly encouraging.† Relaxin acts best when uterine contractions are frequent and forceful. When necessary we have encouraged such contractions with pitocin, which is discontinued when relaxin is started. Treatment was begun when the cervix was dilated to only 2 cm. in diameter and the fœtal membranes were intact. We were able to shorten the 1st stage of labour in primigravidæ, at term, to about 5 hours, in comparison with almost 15 hours in a control group, and about 10 hours in a group treated with pitocin alone. From experience we learned that once dilatation was full, in the relaxin-treated cases, it was necessary to get the patient to the delivery room quickly because the 2nd stage was also shortened (Sands and Ko 1959). These results were obtained with 2 ml. of relaxin.

*Premature Labour*

Abramson and Reid (1955), who first reported the effectiveness of relaxin in the treatment of premature labour, found that the hormone enabled them to prolong pregnancy through the 36th to 40th week. On the other hand, Eichner et al. (1956) were less successful but noted the cervical-softening effect of the hormone, an observation which was corroborated by Hodgkinson when discussing Eichner's paper. Folsome et al. (1956), in a series of forty cases of premature labour, found, however, that the use of relaxin enabled them to prolong pregnancy for up to 10 weeks. Moreover, patients treated

* Based on an address given on Nov. 8, 1957, at the annual meeting of the Canadian Society for the Study of Fertility, London, Ontario.

† The relaxin used in these experiments is known as "Releasin" (Warner-Chilcott).

with relaxin had less pain during labour, and there was a "fourfold greater incidence of painless precipitate delivery". McCarthy et al. (1957) found that relaxin decreased the frequency and regularity of uterine contraction; there was only an occasional mild contraction at the end of 3 to 4 hours, and this could be further controlled by the periodic use of relaxin. The hormone appeared to be ineffective once the membranes had ruptured. Dosage and mode of administration have still to be perfected.

*Retained Dead Fœtus*

In view of the dangerous complication of afibrinogenæmia, a uterus containing a dead fœtus should be emptied as soon as possible. This is not easy because the uterus is singularly unresponsive to the usual methods of stimulation. In fifteen such cases Maclure (1957) successfully emptied the uterus in thirteen. Relaxin, in divided doses, was first given over a period of 12 hours, followed by intravenous pitocin 18-24 hours later. In nine of the thirteen successful cases labour began within an hour. Maclure found that cervical softening was a constant feature and that labour was short, two cases delivering en bloc.

### Uses in Gynaecology

Not many gynæcological conditions lend themselves to treatment with a hormone such as relaxin. Of these, dysmenorrhœa seems to be the one most likely to respond.

Posse and Kelly (1956), using the Karlson tocometer, found that relaxin reduced the amplitude of the fundal contractions which coincided with the severe cramp-like pains of dysmenorrhœa. In just over half the patients who responded, uterine activity ceased completely and pain stopped at the same time. Larkin (1957) found that eighteen out of twenty girls, aged 16, obtained relief from relaxin and he thought that this was "more than a coincidence". Results were also encouraging in a placebo-controlled study of several hundred women working in light industry who suffered from dysmenorrhœa and were treated with relaxin (Abramson and Reid 1958). Over 90% benefited and absenteeism was much reduced.

### Discussion

Not all work with relaxin has produced favourable results, and some investigators have met with complete failure. (Decker et al. 1958, Dill and Chanatry 1958, McGaughey et al. 1958). Premature labour due to disease of the placenta or fœtal death would certainly fail to respond, and in accidental hæmorrhage the use of relaxin is contraindicated. Relaxin is most likely to be effective in premature labour arising from uterine irritability, perhaps by correcting some hormonal imbalance.

Control and shortening of the 3rd stage of labours is now universally accepted and practised. Is there any objection to reasonable shortening of the 1st and 2nd stages? We know that in innumerable cases of precipitate labour there is no damage to mother or child. In our own series, using relaxin, we have managed to shorten the 1st stage to almost a third of the control value without any untoward occurrences, possibly because of the considerable cervical softening and consequently greater productivity of uterine contractions.

The use of relaxin in dysmenorrhœa is being further investigated in young women at university. In addition, the hormone has been found to be active by mouth as well as rectally. Furthermore, depot forms of relaxin already provide prolonged action.

The relaxin-treated woman in labour seems to require less sedation and to complain less of pain. The perineum is very relaxed and she seems to bear her labour with greater equanimity, as if the hormone had an anodyne effect upon the uterus. There is little doubt that the physiological and clinical results warrant extensive study of relaxin.

### Summary

Relaxin seems to have a physiological action upon connective tissue in general and collagen in particular, as shown by "sponge biopsy" studies. It has been used with some benefit in scleroderma and peripheral vascular diseases and during pregnancy it brings about a gradual softening of the normally rigid pelvic joints. Some success has been recorded when it was used in the treatment of dysmenorrhœa whereas, in obstetrics, its principal uses are to arrest early premature labour, to assist in the induction of labour, and to facilitate full-term labour.

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## Parliament

### N.H.S. Estimated Expenditure

In reply to a question in the House of Commons the Minister of Health gave the following figures for the estimated expenditure on the National Health Service in 1959-60 (excluding local health authority expenditure) for England and Wales.

| | £ *million (approx.)* |
|---|---|
| Total Estimated Expenditure | 640 |
| Borne on Exchequer | 475 |
| Met by N. H. S. contributions | 101 |
| Met by Patients' charges | 30 |
| Met by Superannuation contributions and Transfer Values | 33 |

### Drink and Road Accidents

In the House of Lords Viscount Hailsham, the Lord President of the Council, said that a paper summarising the results of experiments on the effect of alcohol on a skill resembling driving, which were conducted under the auspices of the Medical Research Council, was published in the *British Medical Journal* on Oct. 28, 1958. As this report was based on experiments conducted entirely under particular laboratory conditions it did not, in the view of the Minister of Transport and Civil Aviation, in itself provide a basis on which proposals could be framed to extend the use of scientific tests to determine whether a driver is under the influence of alcohol. He was, however, continuing discussions with the Medical Research Council.

# Public Health

## ANTIVACCINIAL GAMMA-GLOBULIN
## A FURTHER REPORT ON SMALLPOX PROPHYLAXIS

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On March 7, one of us (A.B.S.) was asked to see a medical student, who had been ill at home for 6 days and had developed a vesicular rash. A clinical diagnosis was made of moderately severe smallpox, later confirmed by laboratory tests, and the patient was admitted that evening to New Ferry Isolation Hospital. He had been vaccinated successfully 20 years earlier. He made an uneventful recovery from his exanthem, which was shown to be due to the variola major virus. The source of infection was never found, but there was no doubt, either clinically or virologically, that he had smallpox

*The Contacts*

The patient had not left his home during the 6 days before the diagnosis was made, though there had been a number of visitors to the house. His symptoms had started on Feb. 28, and a focal rash appeared on March 2. He had been in an infectious condition, therefore, for 6 days before his removal to hospital.

Four people were particularly at risk. They were, in order of risk: the daily help, last vaccinated 45 years ago; the patient's mother, last vaccinated 43 years ago; the family doctor, vaccinated 57 years ago and revaccinated 36 years ago; and the patient's father, vaccinated 49 years ago and revaccinated 17 years ago.

The mother and father had been in daily contact with their son, the doctor had examined the boy at home on several occasions during his illness, and the daily help had visited the bedroom regularly during this period. All four were vaccinated immediately, though this was not until at least the 5th day of exposure, when little protection could be anticipated. Accordingly it was decided to increase their protection by the use of antivaccinial gamma-globulin prepared from hyperimmune serum. This was obtained from the Central Public Health Laboratory, Colindale, and given on March 9 (father, mother, and daily help), and March 10 (family practitioner). They were each given 1·5 g. of gamma-globulin dissolved in 15 ml. distilled water, by deep intramuscular injection.

Each vaccination gave a good primary result, thus demonstrating the low degree of original immunity. Daily visits were made to these four contacts until March 27, which was 20 days after the last date of exposure. All remained perfectly well, without symptoms or signs suggesting infection.

A further contact was a hospital technician who had taken numerous photographs of the patient in his home on March 7, but owing to recent revaccination he was not considered sufficiently at risk to justify the use of gamma-globulin, and was only revaccinated. He became ill on the 11th day after exposure and developed a prodromal rash on the 13th day. He was admitted to New Ferry Isolation Hospital, but a focal rash did not develop.

### Discussion

The serum used was prepared from the blood of newly vaccinated or recently revaccinated adults. Though gamma-globulin has been used extensively in the prophylaxis of virus infections such as measles, german measles, and poliomyelitis, there are only a few references to its use in smallpox.

The most extensive investigation was undertaken in India in 1953 (Kempe et al. 1956), when it was found that eight out of seventy-five close contacts who had been vaccinated contracted smallpox. When antivaccinial gamma-globulin was given to supplement vaccination, however, only two of a similarly exposed group of fifty-six developed the disease.

There were further limited opportunities for investigation in the Tottenham outbreak in 1957 (Hogben et al. 1958), when several primary contacts were given antivaccinial gamma-globulin in addition to vaccination, and none developed smallpox; and in the Bebington outbreak of 1958, when two household contacts greatly at risk contracted only a very mild form of the disease after such protection (Peirce et al. 1958).

Our recent experience adds to the evidence which justifies the use of antivaccinial gamma-globulin in the prophylaxis of smallpox. Of the four persons given this protection, three had not been vaccinated later than 38 years previously, and had been in close contact with a proved case of variola major for over 5 days; vaccination had been performed too late to ensure protection. The fourth (the patient's father) had been revaccinated 17 years previously. Yet none developed any symptoms or signs. In contrast to these cases the hospital technician, who was not considered greatly at risk and was not given gamma-globulin, developed symptoms and a prodromal rash.

Although the preparation of antivaccinial gamma-globulin is a lengthy and complex process, it is desirable that this serum should now be available at all public health laboratories for early use when close contacts of smallpox require protection. There appears to be no disadvantage in giving larger doses, apart from the relative scarcity of the serum, and we suggest that 2-3 g. might protect a vulnerable contact. Doses of 1 g. and 1·5 g. (Peirce et al. 1958) failed to give complete protection to two highly exposed contacts in the Bebington outbreak, though the eruption and illness were greatly modified.

### Summary

A case of smallpox was diagnosed in Liverpool in May, 1959.

Four close contacts, not protected by recent vaccination, were revaccinated 5 days after exposure, and given 1·5 g. of gamma-globulin prepared from hyperimmune serum. None developed any symptoms or signs of smallpox. One close contact, who was not given gamma-globulin, had an abortive attack of smallpox despite recent vaccinations.

Protection with gamma-globulin should now be readily available at public-health laboratories.

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### Vaccination against Yellow Fever

Dried yellow-fever vaccine, which can be stored in an ordinary refrigerator, is now available. The Ministry of Health has suggested to local authorities that centres for vaccination, now numbering 19 in England and Wales, should be increased.

# In England Now

*A Running Commentary by Peripatetic Correspondents*

We peripatetics have always interpreted the phrase "In England Now" rather widely, and, with your indulgent acquiescence, we have often crossed the Channel and described our experiences in such nearby places as New Zealand, Africa, and the darkest United States. When I took up my *Lancet* of June 27 I was flattered, if slightly appalled, to find that you had followed our example and moved your printing to a temporary Hanseatic refuge. I confess that it was a relief to find that like so many distinguished unwilling exiles, *The Lancet* is fairly resistant to foreign influences. Despite its abrupt translation from the Thames to the Weser—apart from an occasional crossed seven—it is clearly sticking to English ways and the English tongue.

* * *

My dentist is very kind and technically superb and he has a great sympathy and understanding for me personally. He never inflicts unnecessary suffering, and when I sit in his chair I have the fullest confidence that he will finish what he has to do as quickly and as gently as possible. I should hate to go to another dentist, who would certainly not understand my needs and might inflict unnecessary pain and suffering while doing a technically inferior job.

On the other hand I have no confidence whatever in my own personal G.P. His knowledge seems to me limited and I suspect that he believes I am neurotic. He is not interested in me or my needs and he always seems to be anxious to get me out of his consulting-room as quickly as possible.

I had always thought my views on dentists and doctors were private, and it came as a surprise to discover when I questioned my patients that each of them thinks that his or her dentist is kind, understanding, and technically skilful. They all told me that on no account would they ever go to a strange dentist. Unfortunately I cannot ask them what they think of their doctor . . .

* * *

Stereophonic sound is not the only benefit I have had from the new manipulative surgery of the middle ear. Before the operation I was warned that taste might be affected on the same side. After being grateful for the hearing improvement, I noted that salt or granulated sugar rubbed into one side of the tongue might as well be grains of sand, and lemon juice just so many drops of water. I now recognise that this dysfunction, although probably only temporary, has its merits. On the left I can still enjoy the pleasures of a gourmet; but if I happen not to like my food I eat it on the right.

* * *

Chests are best percussed with the patient vertical, and indeed standing. The percussing blow should be brief and brisk and only just strong enough to get a nice note.

These principles I follow. Imagine my astonishment when, at the first tap on the axillary line of a young girl, I saw my patient totter and fall away from me. By grabbing a chair as she rocked towards the floor she just managed to save herself.

Pinking a little, she waved my anxious hand away, and took off her new shoes. Secure once more on the centre of gravity which Nature had given her, she bent down and placed them on the ground, carefully balancing them on their high stiletto heels.

* * *

*In the Garden. — XI*

FULL CIRCLE OR DISEASES OF THE ONION

Sir Robert Walpole said that after dinner
He talked smut so that all the men could join.
Then smut went out and horses were a winner,
Next motor-cars became the common coin.
But now it's u, between the soup and savoury,
To boldly flaunt one's horticultural bravery.
Thus in two hundred years we're back once more
At smut, but now with nothing to deplore.

# Medicine and the Law

### Damages for Loss of One Eye

A WORKMAN, aged 39 at the time of the trial, had been employed in cleaning structural steelwork. In this work he made use of a mechanical wire brush. Because he was not wearing any goggles, a piece of wire from the brush was able to enter his eye, causing injuries which eventually necessitated the removal of the eye; the other eye was unaffected. He claimed damages against his employers, who denied liability.

Mr. Justice Glyn-Jones remarked that he wished to hear argument from counsel on the amount which he should award in damages, for he was of opinion that the conventional amount awarded in such cases was too high.

There were he said, many injuries for which it was customary to award lesser sums, which were in fact more incapacitating—for example, an injury to an ankle which led to permanent stiffness and pain and loss of earning capacity. Would counsel rather lose his sight or his hearing? Counsel said that he would rather lose his hearing, to which his Lordship replied that such an injury was a terrible one: it was like being shut in by a wall of plate glass. Counsel then said that one could not ignore the possibility of the loss of the other eye in this case. His Lordship said that that was an argument which was rarely if ever heard when a man lost a kidney or an ear: in fact the chances of losing the other eye were remote, and the fact that a man only had one eye would mean not only that he would take great care to safeguard it, but that he would choose employment where it was not endangered.

Giving judgment, his Lordship said that the employers were in breach of their duty under the Building Regulations 1948, to provide suitable goggles or effective screens and were also guilty of negligence at common law. The workman was not guilty of contributory negligence. This was an exceptional case in that the loss of one eye had led to a loss of earning capacity which at present was £4 per week. Having regard to the nature of the workman's employment at the time of the accident, it would be quite wrong to award him damages on the basis that he was going to suffer a loss of this amount for the rest of his working life. A lesser sum would be appropriate. In addition to the special damages (i.e., actual pecuniary loss which he had suffered up to the date of the trial), his Lordship would award the sum of £3750 as general damages.

Knight v. T. H. Kenyon & Sons Ltd. — *Queen's Bench Division:* Glyn-Jones J. June 23, 1959. Counsel and solicitors: D. J. Brabin, Q. C., and Hugh Griffiths (W. H. Thompson); G. R. F. Morris, Q. C., and P. J. Crawford (Blount, Petre, & Co.).

GROVE HULL
Barrister-at-law

### A legal correspondent writes:

It is interesting to observe that the learned Judge's award was not in fact much lower than most lawyers would have expected. Conventional damages for the loss of one eye are normally in the region of £2000; the Judge was not prepared to award damages for loss of earnings at the rate of £4 per week, and on the assumption (necessarily speculative) that he regarded £3 per week as the appropriate figure, damages of £3750 are equivalent to £1800 for the loss of the eye (i.e., a solatium for pain and loss of amenity) and 13 years' loss of wages (£1950) at £150 p.a. As the plaintiff was aged 39, it is probable that most Judges would consider a payment of 13 years' earnings in advance an approximation to the true value of a loss of earnings for the rest of the working life. Such a capital sum, invested at 5%, would in fact provide more than 20 years' payment of £150 p.a. before the capital was exhausted.

### Gas-gangrene after an Operation

At Bristol Assizes a man of 53 lost an action for damages against the board of governors of the United Bristol Hospitals.[1 2] He alleged that after amputation of his right little finger for a contracture his hand was too tightly bandaged. Gas-gangrene had developed and two

1. *Manchester Guardian,* June 30, 1959.
2. *Times,* June 30, 1959.

more fingers had to be amputated. The hospital board denied negligence. Giving judgment Mr. Justice Streatfeild said that the plaintiff had suffered a misfortune of the first magnitude. Nevertheless, he was satisfied that no individual had been negligent and that every care had been taken before, at, and after the operation. Surgeons, doctors, and nurses were not insurers, nor were they guarantors of absolute safety. They were not liable in law merely because something went wrong. Their duty was not to have the skill, perception, and knowledge of the topmost specialists, but to exercise professionally that skill and knowledge that belonged to the ordinary practitioner. Judgment was given for the board of governors, and on their behalf it was stated that there would be no application for costs.

## Letters to the Editor

### BOXING

SIR,—According to Mr. Ian M. Leslie (June 20), professional boxing often leads to eventual injury of the brain; but he advocates boxing as a proper sport for boys and young men so long as it is properly controlled. The arguments against boxing are reviewed in your leading article of June 6; but a few words may be added about the young boxer.

Being the neurologist of the Swedish team which studied the immediate effects of head injuries during boxing,[1] I was responsible for the clinical examination. We studied about 65 boxers between 17 and 25 years of age, selected from the 268 who participated in the junior championships of 1950 and 1951. In 14 there were signs of concussion; superficially they appeared to have recovered when they were examined a few minutes after their knockdown, but testing of their orientation, &c., showed the well-known picture of a post-traumatic confusion and amnesia. 9 of the other boxers showed slight symptoms of the same kind.

According to some authorities the knockout is caused by a temporary depression of vasomotor function; this would mean that the loss of consciousness is of a rather innocuous character. The mental confusion observed in our cases, however, cannot be explained by a blackout through a fall of the blood-pressure during the match.

Electroencephalograms, taken before and after the match by the other members of our group, showed marked changes in many of the boxers; and such changes were demonstrated not only after knockouts but also after other hard head blows.

Our conclusion was: "In Sweden, as in many other countries, the risks inherent in boxing have been observed in boxing circles for many years, and restrictions designed to prevent cerebral injuries have been introduced ... the referees are instructed to stop the matches before any more severe punishment occurs, and this applies especially to the Junior matches. These matches also comprise only three rounds of two minutes each. As we have observed in the present investigation, however, this does not prevent the exposure of a large number of these Juniors to slight concussion of the brain which may be repeated during the tournament."

The defective technique of the young boxers and their youthful lack of caution seems to expose them to especially great risks.

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BORIS SILFVERSKIÖLD.

SIR,—Your leading article would have been an exaggerated account of the state of affairs in 1949. Before condemning boxing, as you ask them to do, the profession is entitled to know the state of affairs in Great Britain and Northern Ireland in 1959.

In 1950 the stewards of the British Boxing Board of Control appointed a medical subcommittee to advise them on the medical aspects of boxing, with particular reference to the punch-drunk syndrome. The work of this subcommittee has extended to the issue of instructions and advice to boxers, tournament medical officers, referees, managers, seconds, and other officials so that the then recognised hazards of the sport have been very considerably reduced.

The British Boxing Board of Control controls all professional boxing in Great Britain and Northern Ireland with the exception of that taking place in fairground booths and the following facts refer only to boxing under the jurisdiction of the British Boxing Board of Control.

*Fatalities.*—Since 1946 there have been 4 and 4 only. This out of upwards of 42,000 contests in which some 84,000 boxers were engaged.

*Eye Injuries.*—In 1955 the chairman of the Medical Advisory Board of the New York State Athletic Commission was perturbed by reports emanating from Great Britain of serious eye injuries occurring in boxing, and the medical subcommittee of the British Boxing Board of Control was asked for particulars of these, as they were known not to occur either in the Americas or Continental Europe. Accordingly, seven honorary medical officers of the British Boxing Board of Control were asked to supply particulars of serious eye injuries in their experience. The total number over a period as long as fourteen years was 6. A well-known British consultant has given me permission to use the following extract from a letter written at that time:

> "During three years as a resident and chief clinical assistant at Moorfields Hospital and since my sojourn in . . . which started in 1941, I can only recall two bad eye injuries due to boxing. I have never seen a torn lid, nor have I seen an eye which has been so badly hit as to be in any way injured, apart from these two detachments in myopes".

New York State were accordingly informed that serious injuries to the eye are as uncommon here as they are elsewhere. It should be noted here that when contests are reported as having been stopped because of injuries to the eye, it is invariably because of cuts over the orbit or to the face in the region of the eye.

*The punch-drunk syndrome.*—Boxers in pre-war days, when they were subject to very little medical control and the control of the Board of Control itself was not so strong as it is now, could and sometimes did become punch-drunk. Nowadays, under the jurisdiction of the British Boxing Board of Control, they do not. You suggest that brain damage occurs as a result of knockout blows and punches to the head and that although this brain damage is not apparent immediately it may become so in later years. This, Sir, is pure surmise, but it is quite reasonable to suggest that Nature has provided a reserve of nerve-cells to provide for damage to the brain in the same way as provision is made for the repair of damage in other parts of the body. In 45 years' experience in boxing, I have seen nothing to refute the submission by LaCava[1] that there are two types of knockout. One is a reflex and the other a state of concussion resulting from a series of blows. All the available evidence shows that recovery from the first type is complete, whether it is a result of boxing or otherwise. With rest and abstention from boxing, complete recovery appears to take place in the second type of case also. Unless the injury has been gross neither an electroencephalograph nor the neurologist clinically can detect any abnormality. Nevertheless, in some cases, though not by any means in all, slight damage has occurred and can only—and only then—be detected by the trained observer when the boxer next engages in a contest. If at this stage the boxer is rested, suspended, or in some cases completely retired from boxing, complete recovery appears to take place and it is unfounded speculation to say that signs of the injury may develop years later.

The view of Kaplan and Browder, as described in your editorial is the result of painstaking research over a period of three years, which involved sitting at the ringside during

1. Larsson, L. E., Melin, K. A., Nordström-Öhrberg, G., Silfverskiöld, B. P., Öhrberg, K. *Acta psychiat., Kbh.* 1954, suppl. 95

1. *Brux. Méd.* Jan. 13 and 20, 1952.

innumerable contests with ultra-rapid and ordinary cameras and taking thousands of electroencephalograms before and immediately after contests and during subsequent months. The views expressed may be "rosy" but they do indicate that brain damage is not essential to boxing. And here the point may be made that there are thousands of ex-boxers who show no signs of brain damage even years after terminating a strenuous career when medical control was practically non-existent.

Amongst the measures of control taken nowadays, in addition to various medical examinations are:

(1) The limitation of the number of contests in which a boxer may take part in a given period.
(2) The limitation of the number of rounds in which boxers under 18, under 20, and under 21 may take part.
(3) The correct immediate treatment of a boxer after a count out.
(4) Control of hæmostatics used.
(5) Prohibition of stimulants.
(6) Prohibition of excessive drying out and Turkish baths before a contest and other abnormal methods of weight reduction.
(7) Ban on myopes boxing.
(8) Prohibition of blows to the back of the head and kidneys.

These measures, together with directives issued to referees, such as that prohibiting a referee to allow a defenceless man to be struck, are already circumventing the possibility of any permanent brain damage, just as the punch-drunk syndrome has been eliminated from professional boxing under the Board of Control. We do not pretend to have reached finality, but in the face of what has been done and can still be done, it seems absurd to ask medical men to support a campaign for the abolition of a sport which, when properly controlled, encourages physical fitness, mental alertness, self-confidence and self-control, courage, and chivalry to the good of the individual and the nation as a whole.

Further safeguards are in the course of being implemented by the Board of Control.

If any medical man has any constructive suggestions to make, the medical subcommittee of the Board will be glad to have them. Until such time as some of the alleged evils can be shown to be happening now, the medical profession will only hold itself up to ridicule by exaggerated accounts of them.

The medical control of boxing is becoming stronger throughout the world. Unfortunately, there are still areas where it is not as strictly enforced as in Great Britain and there will never be a law which will prevent a boxer ignoring advice and hiring himself out as a sparring partner, boxing in unlicensed premises, or under the jurisdiction of controlling bodies which are not so strict as the British Boxing Board of Control.

London, W.1. J. W. GRAHAM.
Chairman, Medical Committee, British Boxing Board of Control, and President, European Boxing Union Medical Commission.

*** We never doubted that the hazards of boxing can be and are reduced by Boards of Control: what concerns us is that as long as the boxer is allowed to hit above the clavicle he will, if he can, knock his opponent unconscious by blows to the head. Accidental head injuries severe enough to cause loss of consciousness are today very common and are, we believe, regarded as anything but trivial by most doctors, who know that grave mental disturbance may follow a single apparently minor head injury. The boxer faces a succession of such injuries, deliberately inflicted. It may be impossible to measure latent cerebral injury until many years after the initial damage; and the risk of such injury in boxing seems to us great enough to justify action now, rather than wait, as Colonel Graham asks, until the risk has been accurately assessed. — ED. L.

SIR,—May I develop another approach to this matter? First and last, the man who resorts to violence in order to resolve his day-to-day problems is a pinheaded unteachable; at best he will spend his days driving a road-drill, swinging on the back of a municipal dustcart, or battling for bending money with the mass of the mediocrities. If, on the other hand, finding himself equipped with a superb physique and a quick reaction time he refuses to accept the uniformity of the herd existence and has the courage to face the hard life and rigid discipline which a professional boxing career imposes, it seems a pity to deprive him of his main if not only asset—the opportunity to earn more money than his mental equipment could ever command for him. And with proper safeguards many achieve this.

If, however, his career be less fortunate, as is often the case, there is still no need to suppose that he will finish up as a drunken wifebeater. He is more likely to continue through life as a Turkish-bath attendant or "chucker-out" and finally night-porter, and to end his days as an amiable old silly whose greatest danger to society is his fund of boring stories of the good-old-days and of how and when he beat the great so-and-so in so many rounds.

Today it would seem that the witless coward with his cosh and flick knife receives less condemnation from the courts than your leader extends to the professional boxer, prototype of the old-timer gladiator, who is using his skill and courage to earn himself a little extra money and sometimes even fame.

Finally, may I add that I write this letter supported by a measure of personal authority? My own boxing career was short but vigorous, covering the twelve years of school and university.

It is possible, if not probable, that I should be less stupid than I am had it not been for the many punches that impinged on the Parker head during those years, but I am persuaded that this is a small price to pay for the exciting memories of the ring, and I believe that the mental and physical discipline demanded in those training years have stood me in good stead in the succeeding thirty.

London, W.1. GEOFFREY PARKER.

## AN EPIDEMIC OF UNKNOWN AETIOLOGY

SIR,—In your issue of May 30 Dr. Laidlaw described the clinical features, course, and age and sex distribution of an outbreak of illness of unknown ætiology. As the symptomatology, clinical course, time of year, and indeed all the reported features correspond to the well-documented condition "epidemic, seasonal, or winter vomiting", reports of which are fairly numerous [1-6], one has at least a title for the condition even though its ætiology is still obscure.

Divisional Health Offices, Ashton under Lyne. ALAN S. SIMPSON.

## PATHOGENESIS OF GASTRIC ULCER

SIR,—I was interested in the article by Dr. Marks and Professor Shay (May 30) and in Mr. Bracey's letter (June 6). Obviously a number of anatomical peculiarities are present in the stomach wall which may be of ætiological importance. The distribution of the pyloric mucosa is an attractive explanation of the restriction of ulceration to the distal part of the stomach. That these ulcers occur only on the lesser curvature may be due to a second factor, the fixity of the mucosa along the *Magensterasse*. Aschoff made no measurement of this fixity: if he had he would have discovered not only a gross difference in the mobility on the greater as compared to the lesser curve, but he would have found that the mobility on the lesser curve was varied. It is least mobile in exactly that area where ulcerations are most frequent.[7]

Bromsgrove General Hospital. F. S. A. DORAN.

1. Reimann, H. A., Hodges, J. H., Price, A. A. *J. Amer. med. Ass.* 1945, **127**, 1.
2. Webster, R. C. *Med. Offr.* 1953, **90**, 39
3. Simpson, A. S. *ibid.* 1954, **91**, 175.
4. Silverton, M. I. *ibid.* 1952, **88**, 215.
5. Dummer, F. H. M. *ibid.* 1953, **89**, 65.
6. Goodall, J. F. *Brit. med. J.* 1954, i, 197.
7. Doran, F. S. A. *J. Anat.* 1957, **91**, 573.

## APPLIANCES FOR THE PRODUCTION OF ARTIFICIAL VOICE

SIR,—An electric vibrator can be used to produce a combination of noise and vibration when held against the soft tissues of the neck, in the region of the floor of the mouth. It transmits readily intelligible speech in a monotone. I have devised an instrument for this purpose which is powered by a small six-volt accumulator with a mains unit for use in the home and for recharging the battery. It is chiefly of value to those patients who, having undergone total laryngectomy, are unable to master the art of œsophageal speech.

Œsophageal speech is the ideal and, in my view, is heard at its best in France. Although most British people can master it, there are a few of every nationality who are unable to obtain a satisfactory result, and for them this type of instrument is the only satisfactory alternative.

The aid is of the fixed-frequency pattern, and proved much more reliable than variable frequency and motor-driven models which were tried in the early stages of development. It is interesting to note that the requisite frequency is far lower than the band for the conversational voice on the audiometer. Unfortunately, my research grant did not permit me to complete a collar pattern which would have held the instrument against the neck.

This instrument should help speech therapists in all centres where major laryngeal surgery is undertaken, and it might even be found helpful in teaching the deaf mute.

Production has now started, and further particulars can be obtained from Messrs. Spembly Ltd., New Road Avenue, Chatham, Kent.

I should like to express my gratitude to the South-East Metropolitan Regional Hospital Board for a grant, and also to Sir Charles Harington, Dr. T. S. Littler, Messrs. Dawe Instruments Ltd., Mr. C. S. Whitehead, and Mr. P. Wellen whose enthusiasm made the manufacture of this instrument possible.

Maidstone, Kent. WILLIAM MACGREGOR.

SIR,—A new appliance has lately been described whereby laryngectomised patients who fail to acquire oesophageal voice may be helped to produce voice by artificial means.[1] It consists of an electrically vibrated diaphragm built into the palate of an upper dental prosthesis. It may perhaps interest your readers to mention a few features of its use.

The appliance offers two main advantages over previous artificial speech-aids.

First, the source of sound is placed within the oral cavity. In other appliances where the sound originates outside the mouth and is conveyed to the oral cavity by tube or conduction through the tissues only a fraction of the sound produced can be modulated into speech. In the new appliance all the sound from the diaphragm is used as voice and a very high level of intelligibility is attainable.

Secondly, because the diaphragm is worn as part of a dental prosthesis it is unnecessary to hold any part of the appliance near the mouth while speaking. Thus, it is relatively inconspicuous and convenient to use.

The appliance has now been on trial for the past seven months, and seven patients have been fitted. Two main points emerge from this limited experience.

First, patients vary very much in the ease with which they gain fluency, and intelligence is probably the main factor determining success. One patient required virtually no instruction and his speech was at once understood without difficulty. Other patients have needed to be taught to use the appliance, and unless speech-training facilities are available the full benefit of the appliance may not be obtained.

Secondly, due partly to the quality of voice produced and partly to temperamental differences, men seem to take more readily than women to the appliance and to make fuller use of it.

Some important refinements have lately been made. The convenience of the appliance has been further increased by making the flex easily detachable. It need only be attached to the prosthesis during speech. Also, a new method of sealing the diaphragm has improved the volume and quality of voice. If any of your readers wish to prescribe the appliance, I shall be glad to give them information about the improvements in design.

Rickmansworth, Herts. R. V. TAIT

1. Tait, R. V. *Brit. dent. J.* 1959, **106**, 336.

## EMIGRATION

SIR,—After a recent spate of discussion on this subject may I offer some advice to prospective émigrés, as seen from the western provinces of Canada?

Firstly, few of the provinces here have reciprocity, and the attainment of this may take six months. Embryo specialists should realise that despite their membership they will also have to take the Canadian certification or fellowship. Requisites for these examinations may be obtained from the Canadian Royal Colleges in Ottawa.

Secondly, advertised offers of positions do not always live up to their expectations. Despite all statements to the contrary, standards of living are lower here than in Britain, and the dollar is worth about half the publicised value.

Thirdly, standards here vary and immigrants may become despondent should they discover that the initial welcome has feet of commercial clay.

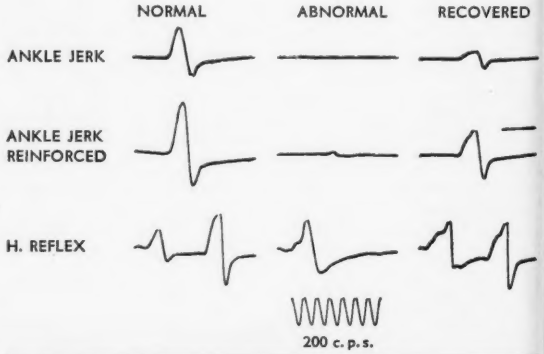
Frankly, doctors contemplating leaving would be well advised to consult good friends in the prospective area, and as far as the prairies go I would be pleased to offer help.

Breton Clinic,
North Battleford, Saskatchewan. DAVID NICHOLSON

## LOSS OF ANKLE-JERK

SIR,—While one of us was recently suffering from sciatica, the opportunity was taken to examine the mechanism of loss of the ankle-jerk. The attack was of moderate severity, but without weakness or sensory loss.

The illustration shown the results obtained, using methods previously decribed,[1] on the normal and affected sides at the height of the attack, and on the affected side some three weeks




1. Buller, A. J., Dornhorst, A. C. *Lancet*, 1957, ii, 1260.

later during recovery. Both mechanically and electrically induced responses were virtually lost while a direct response was easily obtained. At the height of the attack a just-detectable response was obtained on reinforcement, and during recovery, although the reflex had not returned to normal, reinforcement was fully effective.

Spontaneous pain was almost absent during the actual recording, and there was no hyperæsthesia to the shock. It seemed unlikely that there could have been any pathological afferent inflow sufficient to depress the reflex.

We interpret these findings as showing that the reflex was interrupted on the sensory side, neither the alpha nor gamma efferents being probably affected.

We were struck by the absence of any motor disability in spite of almost complete interruption of the reflex arc, and cannot help doubting the importance of the monosynaptic reflex or of the " gamma servo "[2] in human movement.

St. Thomas' Hospital Medical School, London, S.E.1. A. J. BULLER
A. C. DORNHORST.

2. Merton, P. *in* The Spinal Cord. London, 1953.

## Obituary

### LASAR DUNNER

M.D. Berlin

Born in Cologne in 1885, Dr. Dunner came to England as a refugee before the war. In 1940 he took an appointment under Dr. David Diamond at the tuberculosis dispensary in Hull, where his extensive knowledge of tuberculosis and other chest diseases made him a valued member of the staff.

During the late 1930s, Diamond had begun to collect case-histories of boiler-scalers who showed evidence of pneumoconiosis, and in consequence Dunner became interested in industrial chest diseases. After Diamond's death during a bombing raid, Dunner took over the investigation, and he produced a series of papers on occupational disease of the lungs in boiler-scalers. Afterwards, with his colleagues Dr. Robert Hardy, Dr. Richard Hermon, and Mr. D. J. T. Bagnall, he took advantage of the wealth of clinical material in Hull: their papers on lung disease in workers exposed to the dusts of graphite and ultramarine were followed by observations on the effects of sulphur dioxide and fumes of coke fires on the lungs, as well as by studies of dockers who handle grain and seeds. He also wrote on iron fettlers' pneumoconiosis. Apart from these contributions to industrial medicine, he published well over a hundred papers on clinical and experimental work in chest diseases. He retained his youthful vigour and inquiring mind, and at the time of his death—which took place when he was on holiday in Germany on June 6—he was preparing an English version of one of his textbooks on the differential diagnosis of lung disease, now in its second German edition. Cosmopolitan and multilingual, he was a man of great charm, a keen traveller, and an inveterate correspondent. He had never visited the United States, but was elected to honorary membership of the American College of Chest Physicians—which gave him much pleasure.

Dr. Dunner came to this country at an age when he could not adapt himself fully to the English atmosphere and personalities: he was unmarried, and in some respects he was a lonely figure. But he had courage and persistence, and it was entirely through his efforts that an industrial chest diseases clinic was set up in Hull, where, as honorary medical director, he continued his investigations after retiring from the chest clinic in 1955. Generous and unsparing of himself on behalf of his patients, he will long be remembered in the city and country of his adoption.

Surgeon Rear-Admiral B. Pickering Pick, C.B.E., died on July 3 at the age of 79.

## Notes and News

### CIBA FOUNDATION

At a dinner held at Apothecaries Hall on June 26 to celebrate the tenth anniversary, Sir Henry Dale said that the Ciba Foundation filled a new kind of need and a real one. Deriving its initial stimulus and continuous support from the Swiss firm of Ciba, it existed to promote international cooperation in medical and chemical research—cooperation which included friendly controversy and friendly rivalry, " for unanimity is the last thing we want in scientific research ". Much of its success had come from the choice of its director, and Dr. G. E. W. Wolstenholme headed a staff of " almost apocryphal efficiency and complete devotion ". Replying for the founders, Dr. R. Käppeli said that the list of participants in the Foundation's symposia included the most illustrious names in research from almost every country. The founders wanted to promote research across the barrier of frontiers, and their idealism came of their contact with scientists. Lord Adrian believed that the Foundation was becoming steadily more important as an international centre. The choice of London for its establishment was due as much to Britain's geographical situation as to her standing in the medical world. Though London had some 80,000 beds in hotels, these (remarked Lord Adrian) " are mostly either occupied or not of a kind to invite occupation ": the Foundation gave visiting scientists somewhere to sleep outside the meeting-room. Replying to the toast of The Guests from Overseas, proposed in neurological terms by Sir Russell Brain, Prof. A. H. T. Theorell said that when he was young the connection between so-called pure scientists and manufacturing firms was correct but not cordial. Today the attitude had changed on both sides: firms like Ciba were producing first-rate products on a basis of sound research, and the attitude of the pure scientists had become less pure—to the benefit of all parties. Messrs. Ciba could not have given a better demonstration of the international character of their project than by putting it in London, though their obvious choice was Switzerland. But with all the wisdom of its founders it would have failed but for the masterly way in which it was run.

On behalf of the trustees, Sir Russell Brain presented three books to Dr. Wolstenholme—one of them dated 1706, entitled *Wholesome Advice against the Use of Hot Liquors, especially Tea, Coffee, Chocolate, and Strong Waters.*

Prof. A. von Muralt proposed a toast to Sir Harold Himsworth who had presided over the anniversary symposium. Earlier in the day the Ciba Foundation annual lecture had been given by Prof. Pasteur Vallery-Radot; to whom thanks were expressed by Sir Henry Dale.

### NUTRITION WORK OF W.H.O. AND F.A.O.

The director-generals of both the World Health Organisation and the Food and Agriculture Organisation are advised by a joint expert committee, who report on the technical problems arising out of the work of the nutrition divisions of the two Organisations. The 20 sections of the fifth[1] report of this committee testify to the wide range of the nutritional activities of these United Nations agencies. Notable among past achievements have been the collection and publication of data on food consumption, the establishment of protein malnutrition as an international disease, the inquiry into the distribution of endemic goitre, and the publication of the F.A.O. nutritional studies. More attention is now being paid to the nutritional problems of apparently well-fed countries. Food technology, food additives, diet and atherosclerosis, and intake of calcium and strontium 90 are taking their place beside the classical deficiency diseases as subjects for investigation.

### POSTGRADUATE COURSES IN OCCUPATIONAL HEALTH

More and more firms are asking general practitioners to act as part-time health advisers, and the Ministry of Health feel that some doctors may welcome courses on occupational health to help them to deal with this new development in their work. Courses of this kind can, with administrative propriety, be provided under section 48 of the National Health Service Act and two will be held this autumn: one at the London School of Hygiene and Tropical Medicine (Sept. 28-Oct. 3) and

1. Joint F.A.O./W.H.O. Expert Committee on Nutrition. Fifth report. F.A.O. Nutrition Meetings report series no. 19. Rome, 1958. Pp. 55 Obtainable from H. M. Stationery Office. 3s.